Report of the Advisory Committee on Research on Women's Health

Office of Research on Women's Health and NIH Support for Research on Women's Health Issues

Fiscal Years 2003 & 2004

REPORT OF THE ADVISORY COMMITTEE ON
RESEARCH ON WOMEN'S HEALTH

Office of Research on Women's Health

and

NIH Support for Research on Women's Health Issues

FISCAL YEARS 2003 & 2004

http://orwh.od.nih.gov
http://orwh.od.nih.gov/pubs/complete_ICD_report03_04.pdf

Preface

The Advisory Committee on Research on Women's Health (ACRWH),[1] in concert with the Office of Research on Women's Health (ORWH), and the Coordinating Committee on Research on Women's Health (CCRWH), is pleased to submit to the Director of the National Institutes of Health (NIH) this report describing the comprehensive and coordinated efforts of the NIH institutes and centers to address women's health issues through research and related activities supported in fiscal years 2003 and 2004. This report also provides corresponding information and analysis concerning levels of support for such research and related activities.

In accordance with the NIH Revitalization Act of 1993:[2]

- The Advisory Committee shall be composed of no fewer than 12, and not more than 18 individuals, who are not officers or employees of the Federal Government. The Director of the Office shall make appointments to the Advisory Committee from among physicians, practitioners, scientists, and other health professionals, whose clinical practice, research specialization, or professional expertise includes a significant focus on research on women's health. A majority of the members of the Advisory Committee shall be women.
- The Director of the Office shall serve as the chair of the Advisory Committee.
- The Advisory Committee shall—
  - advise the Director of the Office on appropriate research activities to be undertaken by the national research institutes with respect to -
    - — research on women's health;
    - — research on gender differences in clinical drug trials, including responses to pharmacological drugs;
    - — research on gender differences in disease etiology, course, and treatment;
    - — research on obstetrical and gynecological health conditions, diseases, and treatments; and
    - — research on women's health conditions which require a multidisciplinary approach;
  - report to the Director of the Office on such research;
  - provide recommendations to such Director regarding activities of the Office (including recommendations on the development of the methodologies described in subsection (c)(4)(C) of this section and recommendations on priorities in carrying out research described in subparagraph (A)); and
  - assist in monitoring compliance with section 289a-2 of this title regarding the inclusion of women in clinical research.

[1] See page v for a list of 2005 ACRWH Members
[2] Public Law 103-43, 107, Stat. 22 (codified at 42 U.S.C. 289.a-1) [Sec. 486(287d)(d)].

- The Advisory Committee shall prepare a biennial report describing the activities of the Committee, including findings made by the Committee regarding—
  - — compliance with section 289a-2 of this title;
  - — the extent of expenditures made for research on women's health by the agencies of the National Institutes of Health; and
  - — the level of funding needed for such research.
  - The report required in subparagraph (A) shall be submitted to the Director of NIH for inclusion in the report required in section 283 of this title.

The ACRWH has reviewed the information submitted by the institutes and centers (ICs) contained herein and believes that this report accurately reflects the breadth and depth of research and related activities through which NIH fulfilled its mandate from the U.S. Congress to address women's health issues and women's inclusion in research in FY 2003 and 2004. The information and data in this report were prepared and submitted by each of the NIH ICs and highlight significant research studies, achievements, and initiatives that have contributed to an increased knowledge of women's health. Using criteria supplied by the NIH Coordinating Committee on Research on Women's Health, the NIH Office of Financial Management, the NIH Office for Research on Women's Health, and the U.S. Department of Health and Human Services (DHHS) Office of Women's Health, the ICs have also supplied information on budget allocations for women's health research during the same time period.

In this report, ORWH documents its role in catalyzing multidisciplinary and interdisciplinary research on women's health in concert with the NIH ICs, promoting and monitoring women's inclusion in clinical research, and developing programs to nurture women in biomedical careers and to support women and men in women's health research careers during fiscal years 2003 and 2004. The office describes in some detail its programs to promote women's participation and advancement in biomedical careers through a number of programs carried out in collaboration with professional societies and universities, medical schools, and research institutions nationwide.

The executive summary features program highlights from each IC, as well as analyses of funding of research on specific diseases and conditions presented in tabular format. Full reports submitted by each IC constitute the greater part of this report. Research supported by ORWH during FY 2003 and 2004 is presented in the appendices.

The ACRWH acknowledges the valuable contributions of the NIH Coordinating Committee on Research on Women's Health, which is made up of the directors of each of the ICs (or their designated representatives), in preparing this report. We are also grateful to the many staff members of the institutes, centers, and offices who prepared and reviewed the reports of the ICs. We particularly appreciate the work of the NIH Office of Financial Management in collecting and tabulating the budgetary data published in this report.

Finally, the ACRWH acknowledges the work of the ORWH staff.[3] This report reflects the achievements of ORWH in fulfilling its mission and meeting its responsibilities, as stated in the NIH Revitalization Act of 1993.

Advisory Committee on Research on Women's Health, 2005

Representative	*Title and Affiliation*
Vivian W. Pinn, M.D. Chairperson	Associate Director for Research on Women's Health Director, Office of Research on Women's Health National Institutes of Health Bethesda, Maryland
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Barbara G. Wells, PharmD, F.C.C.P.	Dean and Professor School of Pharmacy University of Mississippi University, MS
Marcelle Willock, M.D., M.B.A.	Dean, College of Medicine Charles R. Drew University of Medicine and Science Los Angeles, CA

Contents

Introduction

Substantial scientific progress in women's health research and research on sex and gender differences was achieved by NIH during Fiscal Years 2003 and 2004. To support this scientific activity, nearly $3.5 billion was spent each year on gender-specific research related to women's health. In addition, $22.2 billion was spent on research that benefits both women and men as either basic or laboratory research or clinical studies that included both women and men. This report describes some of the important scientific achievements and advances in women's health research that have been identified during these two years, including scientific areas where research is yielding important new information about sex and gender differences.

In accordance with the NIH Revitalization Act of 1993,[1] the Office of Research on Women's Health (ORWH) collaborated with NIH staff and members of the Coordinating Committee on Research on Women's Health (CCRWH),[2] to provide these programmatic summaries of NIH research and other efforts related to women's health in FY 2003 and 2004. ORWH also documents its role in catalyzing interdisciplinary and multidisciplinary research on women's health, and developing programs to foster women's participation and advancement in biomedical careers. A complete listing of research and other projects supported by ORWH during FY 2003 and 2004 are included in the appendices.

All of the NIH institutes and centers with grant-making authority have reported progress in basic, clinical and/or translational research that is benefiting girls and women, as well as serving to identify if and when sex/gender differences exist. Information contained in this report documents the NIH contributions to the scientific advances in sex/gender studies and in women's health.

One of the major ORWH research programs is the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR). Eleven SCOR centers provide new opportunities for interdisciplinary research approaches to advancing studies on how sex and gender factors affect women's health. Each SCOR promotes interdisciplinary collaborations and the development of a research agenda bridging basic and clinical research on sex and gender factors underlying a priority health issue. Research priority areas addressed by the new centers include mental health, reproductive health, pain disorders, and urinary tract health. The SCOR program complements other federally supported programs addressing women's health issues. Such programs include the Building Interdisciplinary Research Careers in Women's Health (BIRCWH), the Women's Reproductive Health Research Career Development Centers (WRHR), and numerous NIH RFAs and PAs.

Each of the NIH institutes and centers presents a brief accounting of their scientific advances in the Executive Summary section of this report. More detailed discussion of these advances is included in the Reports of the Institutes and Centers section.

You are invited to read this report in depth so that you can more fully realize the tremendous advancements that have taken place in this 2-year period and the promise for even greater advancements in future years.

[1] Public Law 103-43, 107, stat, 22 (codified at 42 USC [sec. 486 (A)].

[2] See pages 7-10 for a list of the CCRWH members

ORWH Staff Roster, 2003

Vivian W. Pinn, M.D.	Associate Director for Research on Women's Health Director, Office of Research on Women's Health
Joyce E. Rudick	Director, Programs and Management
Lisa Begg, Ph.D.	Director, Research Programs
Lynn Armentrout	Secretary
Angela Bates	Program Analyst
Loretta P. Finnegan, M.D.	Medical Advisor to the Director
Eleanor Hanna, Ph.D.	Associate Director for Special Projects and Centers (CFS)
Teresa Kendrix	Administrative Officer
Kimberly Kurilla-Gray	Secretary to the Director
Clarissa LaSalle	Program Assistant
Mary Lawrence	Program Analyst
Ellyn J. Pollack, M.A., APR	Communications Director

ORWH Staff Roster, 2004

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Rhonda C. Harrison	Program Analyst
Kimberly Kurilla-Gray	Secretary to the Director
Clarissa LaSalle	Program Assistant
Mary Lawrence	Program Analyst
Vicki Malick	Acting Director of Communications and Program Analyst Intramural Program on Research on Women's Health (on detail from OIR)

Advisory Committee on Research on Women's Health, 2003

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NIH Coordinating Committee on Research on Women's Health Representatives, 2003

Institute, Center, or Division	*Representative*	*Title*
NIDA	Cora Lee Wetherington	Women & Gender Research Coordinator
NICHD	Mona Rowe	Associate Director for Science Policy Analysis and Communication
NHLBI	Barbara Liu	Deputy Director, Office of Science and Technology
NCRR	Susan Kayar	Health Scientist Administrator
NIAMS	Julia Freeman	Director, Centers Program
NLM	Valerie Florance	Program Officer
NIGMS	Pamela Marino	Program Director
NIEHS	Anne Sassaman	Director, Division of Extramural Research and Training
NCI	Anna Levy	Deputy Director, Office of Women's Health
NIA	Marta Campbell	Chief, Office of International Activities
NINR	Janice Phillips	Program Director
NINDS	Linda Porter	Program Analyst, Systems and Cognitive Neuroscience Cluster
NHGRI	Karen DeLeon	Program Analyst
NEI	Ellen S. Liberman	Director, Lens, Cataract, and Glaucoma Programs
NIDCR	Maria Canto	Program Director, Population Sciences Program
NIDCD	Lana Shekim	Director, Voice and Speech Program
NIAID	Angela Magliozzi	Women's Health Program Coordinator
NIDDK	Eleanor Hoff	Science Policy Analyst
NIMH	Catherine Roca	Chief, Women's Mental Health Programs
NIAAA	vacant	
NIBIB	vacant	
FIC	Karen Hofman	Director, Advanced Studies & Policy Analysis
CSR	Denise Wiesch	Science Review Administrator
CC	Deborah Dozier-Hall	Assistant Chief, Social Work Department
NCCAM	Heather Miller	Senior Advisor to Women's Health
NCMHD	John Ruffin	Director
OAR	vacant	
OSE	Bonnie Kalberer	Contractor
OC	John Burklow	Director, Office of Communications
OBSSR	Virginia Cain	Acting Director
ODS	Mary Francis Picciano	Senior Nutritionist
OE	Brenda Hanning	Acting Director
OSP	Cheryl McDonald	Senior Medical Officer
OCL	Tom Gallagher	Director
OEODM	Joan Brogan	Deputy Director
OIR	Esther Sternberg	Chief, Section on Neuroendocrine Immunology and Behavior
OPLA	Anne Houser	Senior Legislative Analyst

NIH Coordinating Committee on Research on Women's Health Alternates, 2003

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FIC	Sharon Hrynkow	Deputy Director
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OER	Belinda Seto	Deputy Director
OAR	Susan Wise	Program Analyst
NCMHD	Jean Flag-Newton	Deputy Director
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NLM	vacant	
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NIH Coordinating Committee on Research on Women's Health Representatives, 2004

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OSP	Cheryl McDonald	Senior Medical Officer
OCL	Tom Gallagher	Director
OEODM	Joan Brogan	Deputy Director
OIR	Esther Sternberg	Chief, Section on Neuroendocrine Immunology and Behavior

NIH Coordinating Committee on Research on Women's Health Alternates, 2004

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NIGMS	Paula Flicker	Program Director
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NIBIB	Tinera Fobbs	Program Analyst
CSR	Elaine Sierra-Rivera	Science Review Administrator
OEODM	Rose Pruitt	Federal Women's Program Manager
CC	Walter Jones	Deputy Director for Diversity Operations
OBSSR	Susan Solomon	Senior Advisor
OSP	Lana Skirboll	Director
OER	vacant	
NCMHD	Mireille Kanda	Deputy Director
OCL	Walter Mitten	Community Relations Specialist
OIR	Barbara Vonderhaar	Chief, Molecular and Cellular Endocrinology Section
OAR	Denise Miles	Program Analyst

Office of Research on Women's Health

In 1983 the then Assistant Secretary for Health, Dr. Edward N. Brandt, established the Public Health Service Task Force on Women's Health Issues when he recognized the paucity of data specific to women's health and programs. New concepts for federal initiatives for women's health began to evolve. A 1985 report, the Task Force on Women's Health Issues, delineated a series of criteria for "differentiating a health problem, condition, or disease as a woman's issue."[3] The criteria included:

- diseases or conditions unique to women or some subgroup of women;
- diseases or conditions more prevalent in women or some subgroup of women;
- diseases or conditions more serious in women or some subgroup of women;
- diseases or conditions for which risk factors are different for women or some subgroup of women; or
- diseases or conditions for which interventions are different in women or some subgroup of women.

The report recommended "biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups."

Following the issuance of the report of the PHS Task Force on Women's Health in 1985, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research. This policy, which urged the inclusion of women, was first published in the *NIH Guide to Grants and Contracts* in 1987. Later in 1987, minority and other scientists at NIH recognized the need to address the inclusion of minority populations.

Therefore, in a later 1987 version of the *NIH Guide*, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In 1990 the Congressional Caucus for Women's Issues requested that the General Accounting Office (GAO) conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, in Congressional testimony, indicated that the implementation of the policy for the inclusion of women was lacking, and that the implementation was slow and not well communicated, that gender analysis was not implemented, and that the impact of this policy could not be determined.[4] The GAO testimony also indicated that there were differences in the implementation of the policy recommending the inclusion of minorities, and that not all institutes factored adherence to these policies into the scientific merit review.

The GAO findings concerning the lack of consistent implementation of policies for inclusion of women in clinical trials supported by NIH was the issue that catalyzed NIH to establish the Office of Research on Women's Health (ORWH) within the Office of the NIH Director in September 1990. Since its establishment, ORWH has served as a focal point for women's health research at NIH.

ORWH is under the direction of a Director who:

- advises the NIH Director and staff on matters relating to research on women's health;
- strengthens and enhances research related to diseases, disorders, and conditions that affect women;

[3] *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues*, Public Health Reports: Vol. II, January-February 1985.

[4] National Institutes of Health: Problems in Implementing Policy on Women Study Populations (GAO/T-HRD-90-38).

- ensures that research conducted and supported by NIH adequately addresses issues regarding women's health;
- ensures that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH;
- develops opportunities for and supports recruitment, retention, re-entry, and advancement of women in biomedical careers; and
- supports research on women's health issues.

ORWH and Research on Women's Health

Women's health research continued to expand both in its complexity and its scope in FY 2003 and FY 2004. While ORWH does not have grant-making authority, the office serves as the catalyst and coordinator for activities in the area of women's health research. All of the NIH institutes and centers that have research portfolios support some type of biomedical and behavioral research related to women's health. ORWH also collaborates with the broader scientific, health professional, and advocacy communities to encourage meritorious research on women's health and to implement the recommendations from the *Agenda for Research on Women's Health for the 21st Century*.

To keep the research agenda current, an *ad hoc* Research Subcommittee of the Coordinating Committee on Research on Women's Health (CCRWH) annually reviews the many areas of research opportunities and recommends to ORWH scientific areas that are determined to be of special importance for expanding current initiatives, or for developing new research programs. These areas are reviewed in terms of overarching approaches that apply to each research topic. The recommendations are reviewed for approval by the full CCRWH and by the Advisory Committee on Research on Women's Health (ACRWH) on an annual basis. This list of research priorities is by no means comprehensive, nor is it intended that new studies be limited to only those topics. Rather, the recommended priorities signify areas in which NIH wishes to stimulate and encourage research on women's health, or expand current initiatives in areas of research that are already being addressed but have not received adequate attention. The *ad hoc* Research Subcommittee membership contains representatives from many of the ICs (Appendix B).

ORWH Research Priorities for FY 2003

In FY 2003, as in earlier years, ORWH recognized priority areas for new initiatives or where an increased research focus was needed. For FY 2003, three overarching approaches for research on women's health, including sex/gender differences, were cited:

- Inclusion of females across the life span as research subjects, especially among populations of women at risk or traditionally underrepresented in clinical trials, such as those from diverse cultures, minority populations, girls and adolescents, the elderly, rural women or inner city women, those affected by poverty and low socioeconomic status, lesbians, and women with disabilities;
- Multidisciplinary basic, translational, behavioral, and clinical research relevant to women's health, especially on conditions which may be chronic and/or multisystemic; and
- Integration of chemical and physical sciences, mathematics, bioengineering, bioimaging, and the new high throughput functional genomic, metabonomic, proteomic, and bioinformatic technologies with biological sciences in relation to women's health, including the development of novel synthetic devices and biological approaches for tissue and organ regeneration and repair.

Topical Research Priorities for FY 2003

ORWH is particularly interested in supporting basic, translational, behavioral, and clinical research in women's health, especially to

determine sex/gender differences or other variables. The topical research areas are not listed in priority order (Table1).

- *Sex/gender differences in health and disease and therapeutic interventions at the genetic, molecular, cellular, and functional levels*, such as chromosomal, genetic, gonadal and phenotypic sex, including differentiation and development; sex and age differences, as well as the impact of pregnancy and lactation, in pharmacokinetics, pharmacodynamics, drug efficacy, and adverse effects, including their genetic, molecular, and cellular bases, and the development of new methods of analysis; sex/gender differences in behavioral interventions; and sex/gender differences in treatment choice, compliance, and adverse effects.

- *Healthy living and the prevention of chronic disorders using interdisciplinary approaches to chronic multisystemic diseases with multifactorial etiology*, such as the impact of diet, nutrition, hormones, exercise, and weight patterns; the emerging epidemic of eating disorders, including obesity, utilizing basic mechanistic studies, and prevention strategies, and the psychological, neurobiological, and social impact of addiction to tobacco, alcohol, illicit, and licit drugs.

- *Interdisciplinary approaches to chronic multisystemic diseases with multifactorial etiology*, such as the study of genetic, infectious, environmental, molecular, and/or hormonal factors as they contribute to multisystemic disorders affecting women; and the study of allergic, immune, and/or autoimmune diseases, including resistance and susceptibility genes, environmental influences, mechanisms of sex differences in immunological responses, target organ influence, role of innate immunity, development of surrogate markers, and immune therapy.

- *Mental health and addictive disorders*, such as the study of neurobiological and psychological risk and protective factors, including sex and gender differences, in the development of schizophrenia, mood, anxiety, eating, and addictive disorders; the role of sex/gender differences in the neurobiological and psychological consequences of violence, such as trauma, terrorism and bioterrorism, physical and sexual assault, and elder abuse, including that

TABLE 1

Topical Research Priorities for Women's Health Research, FY 2003

- Sex/gender differences in health and disease and therapeutic interventions at the genetic, molecular, cellular, and functional levels
- Healthy living and the prevention of chronic disorders
- Interdisciplinary approaches to chronic multisystemic diseases with multifactorial etiology
- Mental health and addictive disorders
- Reproductive health
- Infections, including sexually transmitted diseases (HIV/AIDS, human papillomaviruses) and the development of topical microbicides
- Care giving and health-related quality-of-life issues
- Cancer
- Neurobiology
- Complementary and alternative medicine and dietary supplements
- Specific organ systems, including musculoskeletal, gastrointestinal, and urological disorders, and ophthalmic diseases

associated with drug and alcohol abuse by victim or perpetrator; developmental aspects of mental health and addictive disorders, such as pubertal vulnerabilities, postpartum depression, postpartum psychosis, and the role of aging; and sex/gender differences in the role of stress and susceptibility to addiction in addictive, mood, and anxiety disorders, and implications for prevention and treatment.

- *Reproductive health*, such as reducing morbidity from myomas, endometriosis, abnormal uterine bleeding, uterine prolapse, polycystic ovarian syndrome, other gynecologic diseases, and promoting increased contraceptive safety and effectiveness; the prevention, diagnosis, and treatment of pregnancy complications, including infections and inflammation, pre-eclampsia, fetal loss, pre-term delivery, gestational diabetes, the development of neural tube defects, cancer, and the effects of cancer treatment; the role of in utero exposures to environmental agents in postnatal diseases; and research on the menopausal transition, with a focus on quality of life issues and menopausal symptoms.

- *Infections, including sexually transmitted diseases*, such as the evaluation of sexually transmitted infections, including HIV/AIDS, human papillomaviruses, and emerging pathogens; and the development of effective topical microbicides and other means to prevent transmission; and sex/gender differences in HIV/AIDS susceptibility, disease progression, prevention, and management.

- *Care giving and health-related quality-of-life issues*, such as the development and evaluation of effective strategies to improve the health-related quality of life for women and their families, including women's contributions to men's longevity; the effects of care giving on the health of the care giver; and the examination of stress and coping styles in women with multiple/competing societal roles.

- *Cancers in women, particularly lung, colorectal, cervical, ovarian, head and neck, oral cavity, and pharynx*, such as basic, etiological, genetic, and/or molecular studies that will elucidate the role of hormonal, infectious, immune, and environmental influences in carcinogenesis, including the examination of alcohol, tobacco, and illicit drug use and the modifying effects of genetic polymorphisms; and the identification of markers of risk and disease, which can be used as targets for prevention, early detection, and treatment.

- *Neurobiology*, such as the examination of sex and endocrine differences in manifestations of brain health and of brain disorders, especially epilepsy, stroke, Alzheimer disease, Parkinson's disease, and mental and addictive disorders; sleep and other circadian rhythms; and the sex differences in acute and chronic pain conditions or syndromes, such as diabetic neuropathies, chronic and migraine headaches, fibromyalgia, chronic fatigue syndrome, and temporomandibular joint disorders.

- *Complementary and alternative medicines and dietary supplements*, such as building the evidence base for effective complementary and alternative medicines and dietary supplements as women's health products, in cooperation with NCCAM and ODS.

- *Specific organ systems*, such as the disproportionate impact of diabetes on women's risk for cardiovascular, cerebrovascular, and peripheral vascular diseases; musculoskeletal system health, including bone and muscle disorders and conditions due to disease or physiological changes in aging and menopause, and injuries in female athletes; gastrointestinal health disorders, including irritable bowel syndrome, liver disease, and inflammatory bowel syndrome; kidney and urologic health, including end-stage renal disease, eclampsia, diabetes, autoimmune and analgesic-abuse nephropathy, interstitial cystitis and painful bladder syndromes, urinary tract infections, urinary incontinence, and pelvic floor disorders/conditions; and ophthalmic

diseases, including dry eye with and without rheumatic disease, glaucoma, diabetic retinopathy, and the impact of life style and aging on macular degeneration and cataracts in women.

ORWH Research Priorities for FY 2004

Early in FY 2004, the *ad hoc* Research Subcommittee undertook a major revision of the annual NIH priorities for research on women's health. Substantial expansion of the overarching themes, now numbering four, were developed by the subcommittee, and subsequently approved by the CCRWH and the ACRWH. Further, the research priority areas were substantially modified to incorporate the trends for greater inter- and multidisciplinary research and the molecular aspects of emerging scientific areas important to sex and gender analysis.

Overarching Themes for Research on Women's Health in FY 2004

Based on the review by the *ad hoc* Research Subcommittee, four overarching themes for research on women's health were identified to guide researchers and policy makers when planning, designing, implementing, and interpreting the results of research addressing women's health. Furthermore, the FY 2004 Overarching Themes, along with the Research Priorities, signify approaches and areas in which the ORWH wishes to stimulate and encourage research on women's health and the advancement of women in biomedical research careers. For FY 2004, the following overarching themes are recommended:

Life Span – The health of girls and women is affected by developmental, physiological, and psychological factors. Women's lives are marked by a continuum from intrauterine life to the elderly years: infancy, childhood and adolescence, menarche, reproductive life, the menopausal transition, postmenopausal years, the elderly, and frail elderly. Many women's lives and health status are influenced by factors such as work inside and outside the home, care-giving such as childcare and elder care responsibilities, reproductive status, and chronic illness. Each of these may influence health, disease, treatment choices, and response to therapy. Researchers should consider these variables in designing studies related to women's health.

Sex/Gender Determinants – Women are characterized by both sex and gender, as highlighted in the *Agenda for Research in Women's Health for the 21st Century* and the Institute of Medicine report, entitled Exploring the Biological Contributions to Human Health: Does Sex Matter? The term sex refers to being male or female according to reproductive organs and functions assigned by chromosomal complement. Sex factors that contribute to the biological differences include chromosomes, reproduction, and hormones. Gender refers to socially defined and derived expectations and roles rooted in biology and shaped by environment and experience. Gender and sex are important considerations in most areas of research, including psychological, social, and behavioral studies. Consideration of these variables is critical to the accurate interpretation and validation of research affecting women's health. Moreover, these variables determine how similar or different health or disease processes may be between women or between men and women.

Health Disparities/Differences and Diversity – Women are disproportionately affected by some conditions and diseases in terms of incidence, diagnosis, course, and response to treatment. Some populations of women may be at higher risk for adverse disease outcomes because of factors such as: culture, education, access to care, quality of care, and opportunities for inclusion as research subjects in clinical trials and studies. Thus, clinical and basic research should include, but not be limited to, differences noted within environmental and genetic factors, population-specific characteristics such as cultural diversity, racial and ethnic minorities, immigrant status, rural or inner city residency status, effects of poverty or low socioeconomic status, sexual orientation, and physical or mental disabilities.

Interdisciplinary Research – With increasing understanding of the inter-relatedness and complexity of disease, the nature of scientific investigation is shifting to an interdisciplinary collaborative approach. Advances in women's health can be better achieved by promoting partnerships in cross-disciplinary research from basic to clinical and translational research

that involves collaborative interactions with researchers in all areas of academic, private industry, and federal settings, and provides access to the latest scientific tools and technologies.

Research from many perspectives is needed in women's health, including integration of knowledge from disparate sources as well as teams with multiple areas of scientific expertise. Interdisciplinary research can facilitate the integration of basic science, clinical research and translational research, population studies, behavioral and social research, and outcomes research. An additional focus on bioengineering and biomedical informatics, genomics, proteonomics, imaging, industry, and metabolomics is increasingly relevant to research on women's health.

Areas of Interest in Women's Health Research for FY 2004

Within the research continuum, studies that encourage the adoption of basic, clinical, and translational research findings should emphasize important questions that still remain about women's health. This would include fostering more research to identify the best methods to move knowledge gained from basic science research into clinical research and practice in order to improve clinical outcomes. Studies that help to determine the best clinical practices in the care of women, or of men, should be emphasized in order to increase the clinical knowledge base and the ability of women to participate in the management of their health.

In addition, studies that enhance the adoption of clinical research results by health care providers and public policymakers are further steps in advancing women's health research. The value of conveying clinical observations to basic scientists is important. Through a continuum of interdisciplinary collaborations, research can better contribute to the development and evaluation of effective strategies to improve the health-related quality of care and quality of life for women.

Basic, clinical, and translational research should be considered in addressing priority areas in women's health research (Table 2). Some examples may include, but are not limited to:

- Studies of chromosomal, genetic, gonadal, and phenotypic sex in *in vitro* or animal models
- Etiologic mechanisms to elucidate sex differences in cellular, tissue/organ, physiological, and/or immune responses to environmental and infectious agents
- Cellular and molecular studies of the mechanism of action and affects of complementary and alternative medicines and dietary supplements in the treatment of conditions or diseases that differentially affect women
- Studies of the pathogenesis of diseases that differentially affect women, including those affecting behavioral pathways and the endocrine, musculoskeletal,

TABLE 2

Research Priorities for Women's Health Research, FY 2004

- Studies of chromosomal, genetic, gonadal, and phenotypic sex *in vitro* or animal models
- Etiologic mechanisms to elucidate sex differences in cellular, tissue/organ, physiological and/or immune responses to environmental and infectious agents
- Mechanism of action and effects of complementary and alternative medicines and dietary supplements
- Pathogenesis of diseases that differentially affect women, including those affecting behavioral pathways
- Systemic and cellular modeling of biological pathways and systems related to women's health
- Clinical trial methodology, including ethical issues and study designs specific to women
- Mental health issues, including addictive and behavioral aspects
- Studies on new agents for management of menopausal symptoms
- Prevalence and validation of sex differences in diagnosis/therapy of disorders/diseases differentially affecting men and women

autoimmune, urologic, cardiovascular, ophthalmic, and neurobiological systems

- Systemic and cellular modeling of biological pathways and systems related to women's health
- Clinical trial methodology, including ethical issues and study design specific to women, novel recruitment strategies, and novel statistical analysis methodology
- Mental health studies, including physical and physiological stressors, incidence and severity of addictive, mood, cognitive, and anxiety disorders, behavioral studies on the effects of care giving on the health of the care giver and multiple/competing societal role.
- Studies on new agents for management of menopausal symptoms
- Prevalence and validation of sex differences in the diagnosis and treatment of disorders and diseases differentially affecting men and women
- Treatments and other interventions for specific diseases that have enhanced clinical presentation in women, including, but not limited to, diseases of the metabolic, endocrine, autoimmune, urologic, ophthalmic, oral, reproductive, musculoskeletal, neurological, and cardiovascular systems
- Special trans-NIH research collaborations in areas such as chronic fatigue syndrome and uterine fibroids

Special Emphasis Areas for FY 2004

The following are areas of special emphasis for fostering research in women's health and in sex/gender determinants that will address current or emerging gaps in our scientific knowledge. For FY 2004, ORWH was especially interested in fostering research in women's health in the high priority areas of prevention and genetics/pharmacogenomics.

Prevention and Treatment

Increased knowledge of how to prevent conditions and diseases or to better treat them can result in significant improvements in the quality and length of women's lives.

Prevention research spans the continuum from the most basic biological studies to understanding the basis and effects of risk behaviors across the life span, and the interventions to change them. Examples of needed prevention research studies in women's health include, but are not limited to:

- Research to identify and validate biomarkers of disease pathogenesis and risk and their applications to disease prevention, early detection, and treatment, including the development of novel tools
- Studies of the impact of diet, nutrition, hormones, exercise, weight patterns, tobacco, alcohol and drug abuse, and violence on health
- Research on reproduction, from menarche, including pregnancy to the menopausal transition, with regard to the susceptibility to, and protection from, diseases and conditions
- Studies of the factors that are involved in disease initiation and progression in order to develop effective preventive and curative strategies
- Development, testing, and validation of preventive and curative strategies for conditions and diseases, including but not limited to: sexually transmitted diseases, cancer, coronary artery disease, stroke, obesity, musculoskeletal disorders, addictions, and chronic multisystemic diseases
- Studies of the effect of biological, behavioral, cultural, social, economic, and environmental factors on susceptibility to, or protection from, disease

Genetics/Pharmacogenomics

The sequencing of the human genome has provided a resource for research on disease incidence, pathogenesis, and response to treatments. The role of genetic polymorphisms and pharmacogenomics holds promise as exhibited by recent successes for predicting response of individuals to a range of current treatments. Emphasis in this emerging area is

needed on women and the diseases that disproportionately affect them, as well as if and why there may be sex differences. For example:

- Particular emphasis on sex chromosomal differences; genomic areas known to be involved in diseases that disproportionately affect women; the effects of aging (or different ages) on gene expression; and the relationship of these findings to genetic polymorphisms
- Genetic, molecular, and cellular bases for action of pharmacologic agents known to have different effects in women. Examples include the scientific basis for drugs, environmental exposures, devices, and biologics targeted at a particular sex for common diseases; impact of life span, developmental phase, and pregnancy in pharmacokinetics, pharmacodynamics, drug efficacy, and adverse effects; development of novel methods of analysis; and the application of pharmacogenomics to clinical care
- Emphasis on critical windows of susceptibility; the interaction of genetic polymorphisms with diet, drugs, or toxins on the architecture or development of reproductive or other organs; genetic, cellular, and molecular mechanisms of environmental exposures occurring prenatally, during puberty or pregnancy, and beyond

Research Funded or Co-Funded by ORWH, FY 2003 and 2004

ORWH does not have grant-making authority, but partners with the NIH institutes and centers to co-fund meritorious projects that advance the mission and scientific priorities of the office and add to the growing body of evidence about women's health and sex and gender differences. These studies aid in the understanding of disease etiology, prevention, detection, treatment, and follow-up. The annual NIH research priorities serve as a guide to select meritorious grants to support with the ICs. Additionally, the grants selected emphasize emerging areas of interest and importance to women's health research.

Tables 3 and 4 highlight the research grants that ORWH supported with the NIH ICs for FY 2003 (Table 3) and FY 2004 (Table 4). Research summaries for FY 2003 and FY 2004 are in Appendices C and D, respectively.

In both FY 2003 and FY 2004, ORWH collaborated with NIH ICs, plus the Agency for Healthcare Research and Quality (AHRQ), to fund or co-fund meritorious research grants and contracts. Research support is distributed across all the major scientific areas, including a focus on health disparities. Multiple grants were supported by ORWH in the areas of aging, alcohol and other substance abuse, cardiovascular disease, diabetes, cancer, gastroenterology, genitourinary, HIV/AIDS, infectious diseases, physical activity, ophthalmic disorders, mental health, obesity/overweight, nutrition, immunity/autoimmunity; musculoskeletal disorders and diseases; reproductive health/developmental biology, including menopause-related topics and uterine fibroids; craniofacial disorders, such as temporomandibular joint dysfunction (TMJ); and the general area of pain control.

The research funded by ORWH addressed the full range of a woman's life span, from the prenatal period to advanced age and frailty. Evaluation of sex/gender differences and health disparities were prominent throughout the total research grant portfolio. ORWH and NICHD co-funded eight new research grants focusing on uterine fibroids research through an RFA on basic science and translational research of leiomyomata uteri (uterine fibroids). Uterine fibroids are an extremely prevalent condition, with severe morbidity seen in many women, including health disparities that exist in certain subpopulations of women. There are also disparities in the number of hysterectomies that may be performed for this condition by region and race/ethnicity. Therefore, research is addressing the gaps in knowledge about the pathobiology of uterine fibroids and better ways to manage them. Further, ORWH funded a study with AHRQ to delineate alternatives to hysterectomy in order to better understand ways to reduce this very common surgical procedure.

Additional health disparities research includes several grants co-funded with NICHD through the Cooperative Reproductive Sciences Research Program at minority institutions.

TABLE 3
ORWH Co-Sponsored Research Initiatives, FY 2003

Subject	*Title*	*IC*	*Award Amount*
Adolescent Health	Mothers Living with HIV and Their Adolescent Children	NIMH	$ 300,000
Aging	Aging of Brain: Effects of Prenatal Nutrition	NIA	100,000
	A Fall Prevention Program for High-risk Elderly Women	NINR	100,000
	Role of Estrogen in the Pathogenesis of Tubulointerstitial Disease in Aging	NIA	77,600
	Relaxation Therapy for Alzheimer's Caregivers	NINR	99,999
	Custodial Grandparents and Religion and Spirituality	NIA	61,800
	Health, Illness, and Social Life at Older Ages National Social Life Health and Aging Project	NIA	250,000
Alcohol and	Alcohol, HIV-Risk Behaviors, and Sexual Victimization	NIAAA	50,000
Other Substance	Effects of Smoked Heroin Across the Menstrual Cycle on Cessation	NIDA	298,391
Abuse	Gender Differences in Drug Abuse	NIDA	291,889
	College Women: The Alcohol and Victimization Link	NIAAA	100,000
	Reducing Alcohol and Risks Among Young Females	NIAAA	150,000
Cancer	Clinical Trials of Two Human Papillomavirus-Like Particle Vaccines	NCI	600,000
	RCT of Plant-based Diet in Breast Cancer Recurrence	NCI	100,000
Cardiovascular	Genetics of Early-onset Stroke	NINDS	300,000
Disease	Altered Glucose and Lipid Metabolism in Obesity and Cardiovascular Disease	NHLBI	200,000
Craniofacial	Brief Focused Treatment for TMD: Mechanisms of Action	NIDCR	100,000
	Genotype and TMJD Vulnerability Types	NIDCR	100,000
	Neuronal Plasticity Related to TMJ and Fibromyalgia	NIDCR	100,000
	Estrogen Regulation of Inflammation Related to Temporomandibular Joint Disorders and Diseases	NIDCR	100,000
	International Research Registry Network for Sjögren's Syndrome	NIDCR	200,000
Diabetes	Diabetes Prevention Program Outcomes Study (DPPOS)	NIDDK	300,000
Gastroenterology	Biofeedback for Fecal Incontinence and Constipation	NIDDK	75,000
	Identification and Characterization of SDK Channels	NIDDK	175,000
	Improving IBS Outcomes	NINR	100,000
Genitourinary	Regulation of Renal Xenobiotic Transport by Estrogens	NIDDK	186,345
	Patient-centered Goals for Pelvic Floor Dysfunction	NICHD	74,000
	Weight Reduction for Incontinence Network (WIN)	NIDDK	250,000
HIV/AIDS	Impact of Delivery Models in HIV Health Care	FIC	20,000
	Interventions to Reduce HIV-1 Incidence After Delivery	FIC	20,000
	Family Therapy Mechanisms in HIV-positive Women in Drug Recovery	NIDA	335,609
	Drugs, Gender, and Healthcare Use Among HIV-positive Homeless	NIDA	200,000
	AIDS International Training and Research Program (AITRP)	FIC	50, 000
	Scale-Up of Community-based HIV Prevention and Care	FIC	50,000
	AIDS International Training and Research Program (AITRP)	FIC	50,000
	HIV-1 Shedding from Female Genital Tract	NICHD	253,187

(continued on page 20)

* When supported by more than one IC, only the primary IC is listed.

TABLE 3 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2003

Subject	*Title*	*IC*	*Award Amount*
Immunity/ Autoimmunity	Sex-based Differences in Anti-viral Immunity and Systemic Lupus Erythematosus	NIAID	$ 50,000
	Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Average Pain Sensitivity	NIAMS	900,000
	Mechanism Regulating Neutrophil Activation in Pregnancy	NIAID	50,000
	Sex-based Differences in the Immune Response	NIAID	50,000
	Brain Connections	NIAMS	40,000
	Identifying Genes for Neuropsychiatric Lupus	NIAMS	20,000
	Antibodies to NR2 in SLE	NIAMS	40,000
	Brain Cell Death in MRL Mice: Targets and Mechanisms	NIAMS	100,000
	Virginia Mason/UCHSC Autoimmune Center	NIAID	200,000
	T Cell Reconstitution After Stem Cell Autograft	NIAID	60,000
	How Does Blockage of CD40/CD40L Prevent Autoimmunity?	NIAID	100,000
	Fine Specificity of Scleroderma Autoantibodies	NIAMS	200,000
	Studies of Collagen Gene Regulation in Two Murine Models	NIAMS	200,000
	EBNA-1 in Lupus	NIAID	200,000
	Registry and Repository of African Americans with Rheumatoid Arthritis	NIAMS	200,000
	Inflammation and Cardiovascular Disease in Rheumatoid Arthritis	NIAMS	99,999
	UCSF Autoimmunity Center of Excellence	NIAID	60,000
	Treatment of Autoimmune Disease by Cost Costimulatory Signal	NIAID	60,000
	Suppression and Exacerbation of B- and T-Cell Responses	NIAID	60,000
	Modulation of B-Cell Responses in Autoimmunity	NIAID	60,000
	UAB Autoimmunity Center for Excellence	NIAID	60,000
	Autoimmunity Centers of Excellence	NIAID	278,506
	An Animal Model for Graves' Disease/Ophthalmology	NEI	126,000
Infectious Diseases	Sex in Viral Myocarditis	NIAID	50,000
	Seroprevalience/Incidence of Genital Herpes	FIC	20,000
Menopause	Study of Women's Health Across the Nation II (SWAN II)	NIA	250,000
	The Study of Women's Health Across the Nation (SWAN II) Sub/Pilot Projects	NIA	202,756
	Menopausal Depression: Chronobiologic Basis	NIMH	100,000
	Centers for Dietary Supplements Research: Botanicals	NCCAM	100,000
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	200,000
	Baseline Measurements for Effects of Soy on Bone, Cancer, and Cognition Health	NCCAM	48,000
Mental Health	Health Survey of Two-Spirited Native Americans	NIMH	175,000
	Stress Response Differences in Females: Estradiol's Role	NIMH	74,350
	CARE Intervention for Depressed Mothers and Their Infants	NINR	100,000

(continued on page 21)

TABLE 3 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2003

Subject	*Title*	*IC*	*Award Amount*
Musculoskeletal Systems	Osteoarthritis Initiative	NIAMS	$ 800,000
	Glucocorticoids Alter the Birth and Death of Osteoblasts	NIAMS	100,000
	Low-dose Doxycline Effects on Osteopenic Bone Loss	NIDCR	324,398
	Factors Affecting the Bone Response and Non-response	NIAMS	99,999
	Ethnic Differences in the Management of Osteoarthritis	NIAMS	300,000
	Longitudinal Changes in Hip Geometry and Skeletal Muscle	NIAMS	222,980
	Bone-Sparing by Ca Salts with and without Extra Phosphorus	NIAMS	75,000
	Calcium Absorption in Caco-2 Cells: Molecular Mechanism	NIDDK	200,000
	Bone-Sparing Effects of Soy Phytoestrogens in Menopause	NIAMS	100,000
Neurology	Sex Differences in Dopamine Systems	NINDS	100,000
Nutrition	Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder	NIDDK	100,000
Obesity/Overweight	Look AHEAD (Action For Health in Diabetes)	NIDDK	100,000
	Dysregulated Muscle Lipid Metabolism in African Americans	NIDDK	139,500
Ophthalmic Diseases	Incidence of Late Macular Degeneration in Older Women	NEI	230,000
	Visual Dysfunction and Quality of Life in Multiple Sclerosis	NEI	125,000
	Effect of Estrogen on Radiation-included Cataractogenesis	NEI	147,367
	Estrogen Receptors and Maintenance of Lens Transparency	NEI	130,093
Pain	Low Back Pain — A Multicenter Randomized Trial	NIAMS	100,000
	Pain Management in Temporomandibular Joint Disorders	NIDCR	312,313
	Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)	NIDCR	100,000
	Sex Differences in Opioid Analgesia	NIDA	50,000
	Trigeminal Pain Mechanisms and Control	NIDCR	159,422
Physical Activity	Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease	NHLBI	250,000
	Increasing Physical Activity Levels in Low-income Women	NIDDK	178,750
Reproductive Health/ Developmental Biology	Fragile X Mental Retardation Gene Premutation	NICHD	113,000
	Development and Differentiation in Reproductive Axis Cooperative Reproductive Sciences Research at Minority Institutions	NICHD	250,000
	Intermediate Outcomes of Hysterectomy and Alternatives	AHRQ	250,000
	The Biologic Effects of Androgens in Men and Women	NICHD	200,000
	MMC/PSU Cooperative Center for Research in Reproduction	NICHD	200,000
	Control of Menstrual Bleeding Disturbances in Women	NICHD	35,000
	Female Reproductive Organs and their Innervation	NINDS	100,000
	Protein Tyrosine Kinases in Leiomyomata Uteri	NICHD	300,000
	Estrogen Dependency of Uterine Leiomyoma	NICHD	300,000
	Collaborative Research Initiative	NICHD	150,000
	Prevalence and Etiological Predictors of Vulvodynia	NICHD	100,000
	Vulvodynia Prevalence and Efficacy of Four Interventions	NICHD	100,000

* When supported by more than one IC, only the primary IC is listed.

TABLE 4
ORWH Co-Sponsored Research Initiatives, FY 2004

Subject	*Title*	*IC*	*Award Amount*
Aging	Phytoestrogens and Aging: Dose, Time, and Tissue	NIA	$ 195,000
	Modulation of Age-related Changes in the Auditory System	NIA	315,250
	End-of-Life Care in Assisted Living Facilities	NINR	75,499
	A Fall Prevention Program for High-risk Elderly Women	NINR	100,000
	Health, Illness, and Social Life at Older Ages: National Social Life Health and Aging Project	NIA	250,000
Alcohol and Other Substance Abuse	Screening and Brief Intervention of Problem-drinking Women	NIAAA	100,000
	Alcohol Pharmacogenetics in Mexican Americans	NIAAA	100,000
	Reducing Alcohol and Risks Among Young Females	NIAAA	150,000
Cancer	Culture and Cancer Disparities: The Case of Latino Women	NCI	162,000
	Modulation of a Breast Cancer Pathway	NCI	133,650
	Clinical Trials of Two Human Papillomavirus-like Particle Vaccines	NCI	600,000
Cardiovascular Disease	Genetics of Early-onset Stroke	NINDS	300,000
	Altered Glucose and Lipid Metabolism in Obesity and Cardiovascular Disease	NHLBI	200,000
Craniofacial	Brief Focused Treatment for TMD: Mechanisms of Action	NIDCR	100,000
	Genotype and TMJD Vulnerability Types	NIDCR	100,000
	Neuronal Plasticity Related to TMJ and Fibromyalgia	NIDCR	100,000
	Estrogen Regulation of Inflammation Related to Temporomandibular Joint Disorders and Diseases	NIDCR	100,000
	International Research Registry Network for Sjögren's Syndrome	NIDCR	200,000
Diabetes	The Role of Inflammation and Parity on GDM and Type 2 DM	NIDDK	100,000
	Estrogen Effects in Insulin Target and Granulosa Cells	NIDDK	100,000
	Diabetes Prevention Program Outcomes Study (DPPOS)	NIDDK	300,000
Gastroenterology	Improving IBS Outcomes	NINR	100,000
Genitourinary	Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome	NIDDK	350,000
	Risk Factors for Decline in Renal Function	NIDDK	100,000
	The Function of the Urethra in Continent Women	NICHD	97,054
	Weight Reduction for Incontinence Network (WIN)	NIDDK	250,000
HIV/AIDS	Impact of Delivery Models in HIV Health Care	FIC	20,000
	Interventions to Reduce HIV-1 Incidence after Delivery	FIC	20,000
	AIDS International Training and Research Program (AITRP)	FIC	50, 000
	Scale-up of Community-based HIV Prevention and Care	FIC	50, 000
	AIDS International Training and Research Program (AITRP)	FIC	50,000

(continued on page 23)

TABLE 4 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2004

Subject	*Title*	*IC*	*Award Amount*
Immunity/ Autoimmunity	Innate and Adaptive Regulatory T Cells in Immune Tolerization of Rheumatoid Arthritis	NIAID	$230,375
	Mitochondrial Dysfunction in Patients with Systemic Lupus Erythematosus	NIAID	152,000
	Sex-Based Differences in Anti-Viral Immunity and Systemic Lupus Erythematosus	NIAID	50,000
	Mechanism Regulating Neutrophil Activation in Pregnancy	NIAID	50,000
	Sex-Based Differences in the Immune Response	NIAID	50,000
	Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Average Pain Sensitivity	NIAMS	400,000
	Brain Connections	NIAMS	80,000
	Identifying Genes for Neuropsychiatric Lupus	NIAMS	40,000
	Antibodies to NR2 in Systemic Lupus Erythematosus	NIAMS	60,000
	Brain Cell Death in MRL Mice: Targets and Mechanisms	NIAMS	20,000
	Virginia Mason/UCHSC Autoimmune Center	NIAID	200,000
	How Does Blockage of CD40/CD40L Prevent Autoimmunity?	NIAID	100,000
	Fine Specificity of Scleroderma Autoantibodies	NIAMS	200,000
	Studies of Collagen Gene Regulation in Two Murine Models	NIAMS	200,000
	EBNA-1 in Lupus	NIAID	200,000
	Registry and Repository of African Americans with Rheumatoid Arthritis	NIAMS	200,000
	UCSF Autoimmunity Center of Excellence	NIAID	60,000
	Treatment of Autoimmune Disease by Co-Stimulatory Signal	NIAID	60,000
	Suppression and Exacerbation of B- and T-Cell Responses	NIAID	60,000
	Modulation of B-Cell Responses in Autoimmunity	NIAID	60,000
	UAB Autoimmunity Center for Excellence	NIAID	60,000
	An Animal Model for Graves' Disease/Ophthalmology	NEI	126,000
Infectious Diseases	Sex in Viral Myocarditis	NIAID	50,000
	Seroprevalience/Incidence of Genital Herpes	FIC	20,000
Menopause	Effects of Botanicals on Cognition in Midlife Women	NCCAM	194,837
	Study of Women's Health Across the Nation II (SWAN II)	NIA	250,000
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	200,000
Mental Health	Evidence-based Practice Report on Eating Disorders	AHRQ	250,000
	Estrogen Influences on Neural Precursor Cell Development	NIMH	222,179
	Brain LC-PUFAs and Maternal Mental Health	NIMH	243,827
	Health Survey of Two-Spirited Native Americans	NIMH	175,000
Musculoskeletal Systems	Regulation of PTH Activity in Bone by B-arrestin	NIAMS	99,999
	Osteoarthritis Initiative	NIAMS	800,000
	Glucocorticoids Alter the Birth and Death of Osteoblasts	NIAMS	100,000
	Low-dose Doxycycline Effects on Osteopenic Bone Loss	NIDCR	384,609
	Bone-sparing by Ca Salts with and without Extra Phosphorus	NIAMS	75,000
	Bone-sparing Effects of Soy Phytoestrogens in Menopause	NIAMS	100,000
Obesity/Overweight	Longitudinal Assessment of Bariatric Surgery (Expansive)	NIDDK	300,000
	Look AHEAD (Action For Health in Diabetes)	NIDDK	100,000

(continued on page 24)

* When supported by more than one IC, only the primary IC is listed.

TABLE 4 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2004

Subject	*Title*	*IC*	*Award Amount*
Ophthalmic Diseases	Incidence of Late Macular Degeneration in Older Women	NEI	$230,000
	Estrogen Receptors and Maintenance of Lens Transparency	NEI	131,297
Pain	Mast Cell Role in Masseter Muscle Repair	NIDCR	150,000
	Hormonal Cycles in Women: Effects on Temporomandibular Disease and Disorder Pain and Symptoms	NIDCR	130,000
	Twin Study of Chronic Widespread Pain	NIAMS	99,999
	Pain Management in Temporomandibular Joint Disorders	NIDCR	341,705
	Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)	NIDCR	100,000
	Sex Differences in Opioid Analgesia	NIDA	50,000
	Trigeminal Pain Mechanisms and Control	NIDCR	163,734
Physical Activity	Social Cognitive Theory and PA after Endometrial Cancer Intervention	NCI	100,000
	Young Adult Environmental and Physical Activity Dynamics	NCI	100,000
	Mediators and Moderators of Exercise Behavior Change	NCI	100,000
	Physical Activity Adherence in Black Women Over 65	NINR	34,228
	Heart to Heart: An Exercise Intervention for Rural Women	NINR	31,569
	Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease	NHLBI	250,000
Reproductive Health/ Developmental Biology	Evidence-based Practice Report on Assisted Reproductive Technology	AHRQ	150,000
	Protein Tyrosine Kinases in Leiomyomata Uteri	NICHD	75,000
	Finding Genes for Uterine Fibroids	NICHD	75,000
	Estrogen Dependency of Uterine Leiomyoma	NICHD	75,000
	Molecular Etiology of Leiomyoma Uteri	NICHD	75,000
	Regulation of Uterine Fibroids by CCN5	NICHD	75,000
	Reactive Oxygen Species Regulate Smooth Muscle Growth	NICHD	75,000
	Leiomyomata Uteri: Apoptosis and Cell Survival Pathways	NICHD	75,000
	Estrogen Biosynthesis and Uterine Leiomyomata	NICHD	75,000
	Pregnancy and Drug Metabolizing Enzymes and Transporters	NICHD	350,000
	Washington Obstetric–Fetal Pharmacology Research Unit	NICHD	150,000
	UW Obstetric–Fetal Pharmacology Research Unit	NICHD	150,000
	Obstetric–Fetal Pharmacology Research Units Network	NICHD	150,000
	Regulation of the Contraction in Human Uterus	NICHD	100,000
	Pregnancy and Drug Metabolizing Enzymes and Transporters	NICHD	150,000
	Molecular Mechanisms of Ovarian Follicular Activation	NICHD	99,999
	Role of Neutralizing Antibodies in Transmission of SHIV	NICHD	99,999
	Development and Differentiation in Reproductive Axis	NICHD	250,000
	Intermediate Outcomes of Hysterectomy and Alternatives	AHRQ	250,000
	The Biologic Effects of Androgens in Men and Women	NICHD	200,000
	MMC/PSU Cooperative Center for Research in Reproduction	NICHD	200,000
	Control of Menstrual Bleeding Disturbances in Women	NICHD	35,000
	Collaborative Research Initiative	NICHD	150,000
	Prevalence and Etiological Predictors of Vulvodynia	NICHD	100,000
	Vulvodynia Prevalence and Efficacy of Four Interventions	NICHD	100,000

* When supported by more than one IC, only the primary IC is listed.

These types of grants are designed to augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions in the area of reproductive health research. ORWH also partners with NICHD on a range of chronic gynecological conditions that affect the quality of life for many middle-aged and older women. In general, these grants focus on the etiology, prevalence, and possible treatment for these chronic conditions.

Chronic pain and pain control continue to be important areas for women's health research. ORWH and NIDCR co-funded several grants and contracts in the area of temporomandibular joint dysfunction (TMJ) disorders. A new FY 2003 grant, co-funded by NIDCR and ORWH, created the first Research Registry and Repository for the Evaluation of TMJ Implants. There are other grants focusing on trigeminal pain mechanisms and control, and pain management studies for TMJ. Additionally, ORWH co-funded with NIDCR a number of grants addressing such topics as estrogen regulation of inflammation related to TMJ, genotype and TMJ vulnerability types, and neuronal plasticity related to TMJ and fibromyalgia. In FY 2003, NIDCR and ORWH co-funded the newly created International Research Registry Network for Sjögren's Syndrome. Within more general pain control issues, ORWH supported valuable research looking at sex differences in opioid analgesia, and a study of twins and chronic widespread pain.

ORWH co-funded menopause-related grants with NIA, NCCAM, and NIMH, including support for the SWAN study (Study of Women Across the Nation), the landmark study of the natural history of the menopausal transition. Because this cohort represents a multiracial and multicultural group, important insights are being identified that will be informative to women and their physicians. across. Among other menopause-related supported by ORWH is a study underway with NIMH on menopausal depression.

ORWH and NCCAM are partnering on several grants that focus on botanical products or complementary and alternative methods to treat symptoms associated with the menopause. Additional areas of focus include the effects of botanical products on a woman's cognition and whether there is any impact on the progression of atherosclerosis, which is a major disease outcome in postmenopausal women.

Since its early years, ORWH has co-funded a number of grants with NIAID to advance the understanding of the underlying causes, complications, and treatment strategies for autoimmune disorders. More recently, ORWH, through the Autoimmune Centers of Excellence, co-funded six centers that are studying a wide array of autoimmune disorders. These comprehensive center grants focus on common underlying mechanisms of disease etiology and include translational studies, such as randomized clinical trials of different autoimmune conditions.

As a focal point for women's health research at NIH, ORWH continues to encourage greater attention to autoimmunity, its impact on women of all ages, races, and ethnicity, and participates as a member of the Autoimmune Diseases Coordinating Committee (ADCC). The ADCC, which is Congressionally mandated, is a trans-NIH group that oversees and monitors research progress in this area. Led by NIAID, the ADCC is charged with coordinating and monitoring progress in autoimmune research across NIH, and periodically submits a report to Congress on its progress.

Partnering with NIAID, NIAMS, and NEI, ORWH co-funds a number of other autoimmune grants that focus on conditions, such as systemic lupus erythematosus (SLE), the neuropsychiatric manifestations of SLE, rheumatoid arthritis, Sjögren's syndrome, scleroderma, Graves' disease, multiple sclerosis, and viral myocarditis.

ORWH has had a longstanding commitment to support funding for SLE because of the complex and serious manifestations of this disorder, which is nine times more common in women, particularly women of color. ORWH and NIAMS co-funded several grants exploring the neuropsychiatric manifestations of SLE from a genetic perspective, with the goal of identifying the underlying etiology and progression to this state that may lead to the subsequent identification of innovative treatment strategies. In FY 2004, ORWH teamed with NIAMS to co-fund an important new SLE grant that focuses on the mechanism regulating neutrophil activation in pregnancy. This particular area had not been studied until recently and may provide important insights into ways to reduce pregnancy loss in patients with SLE.

ORWH co-funds with NIAMS the Registry and Repository of African Americans with Rheumatoid Arthritis in order to better understand the pathogenesis and natural history of this disorder in this at-risk population. Another grant supported by ORWH focuses on inflammation and cardiovascular disease in rheumatoid arthritis.

Musculoskeletal conditions, such as osteoarthritis and osteoporosis, contribute significant disability to women of all ages, but especially to women who are postmenopausal or older. ORWH has been a long-term partner and initial co-funder with NIAMS, NIA, and others in supporting the Osteoarthritis Initiative (OAI) in the study of osteoarthritis. The OAI is successfully recruiting its 5,000 study subjects and is expected to serve as a national repository for biological materials about the natural history of osteoarthritis that will guide state-of-the-art treatment strategies. An ancillary study from the OAI is evaluating ethnic differences in the management of this disorder, especially within African American populations.

Osteoporosis is another important concern across the life span of women, including sex and gender differences and differences among different races and ethnic populations. ORWH supports several grants with NIAMS that focus on the longitudinal changes in hip geometry and skeletal muscle, calcium absorption, factors affecting bone response or non-response, bone-sparing effects of soy phytoestrogens, and treatment effects on osteopenic bone loss.

ORWH continues to expand its grant portfolio in other areas of programmatic importance and relevance. These areas include prevention of disease, health promotion, healthy aging, physical activity, nutritional research, and eating disorders, such as obesity. Research on health disparities is a strong focus, especially as it relates to chronic conditions like diabetes, cardiovascular diseases, and obesity.

By the successful collaboration of ORWH with the NIH ICs, the office is able to provide funds to continue studies and further investigations of sex differences in health and disease in many areas, such as irritable bowel syndrome, stroke, the consequences of diabetes, treatments for obesity (such as bariatric surgery), vaccine development to prevent cervical cancer, HIV/AIDS and other sexually transmitted diseases, and the consequences and treatment of substance abuse. Additionally, ORWH co-funded innovative grants that focus on culture and cancer disparities, end-of-life care, fall prevention in the elderly, and care giver research.

Tables 5 and 6 highlight Program Announcements (PAs) and Requests for Applications (RFAs) co-sponsored by ORWH and the ICs during FY-2003 and 2004. ORWH continues to lead two RFAs in the area of career development in women's health research and the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs).

Interdisciplinary Programs

ORWH, with the support and collaboration of the NIH ICs, developed and is the primary sponsor of several new and innovative interdisciplinary research centers and research training programs. These programs, which include BIRCWH, SCOR, WHRH, and other Special trans-NIH initiatives, have benefited both women's and men's health through sex and gender research, interdisciplinary scientific collaboration, and support for young investigators in a mentored environment to become independent researchers in women's health.

Building Interdisciplinary Research Careers in Women's Health

The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program supports junior faculty members who have recently completed clinical training or postdoctoral fellowships, and who are beginning basic, translational, clinical, and/or health services research related to women's health. The program pairs junior researchers with senior investigators in a mentored environment. Women and minority investigators are encouraged to apply. The initial BIRCWH was awarded in FY 1999 and has continued through FY 2004. Its success in developing Interdisciplinary Women's Health Research (IWHR) Scholars.

TABLE 5

Request for Applications and Program Announcements Sponsored by ORWH, FY 2003

Building Interdisciplinary Research Careers in Women's Health (BIRCWH I)
(ORWH, NIA, NIAAA, NIAID, NIAMS, NCI, NICHD, NCCAM, NIDCD, NIDR, NIDDK, NIDA, NIEHS, NINDS, AHRQ) (RFA-OD-99-008)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH II)
(ORWH, NIA, NIAAA, NIAMS, NICHD, NIDR, NIDDK, NIMH, ODS, AHRQ) (RFA-OD-02-001)

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORS)
(ORWH, NIAMS, NICHD, NIDR, NIDDK, NIDA, NIEHS, NIMH, FDA) (RFA-OD-02-002)

Leiomyomata Uteri: Basic Science and Translational Research
(ORWH, NICHD, NIEHS) (RFA-HD-03-005)

Stigma and Global Health Research Program
(ORWH, FIC, HRSA, NCHMD, NHGRI, NIAID, NIDCR, NIMH, NINDS, NIAAA, NIDA, OAR, OBSSR, CIHR, INMHA, IDRC) (RFA-TW-03-001)

Women's Reproductive Health Research Career Development Centers
(ORWH, NICHD) (RFA-HD-03-020)

Phase II International Clinical, Operational, and Health Services Research Training Awards for AIDS and Tuberculosis (Comprehensive ICOHRTA AIDS/TB)
(ORWH, FIC, NIAAA, NIAID, NICHD, NIDA, NIMH, NINDS, CDC, USAID) (RFA-TW-03-003)

Pathobiology of Temporomandibular Joint Disorders
(ORWH, NIDCR, NIAMS) (RFA-DE-03-005)

Global Health Research Initiative Program for New Foreign Investigators
(ORWH, FIC, NCI, NEI, NHLBI, NIBIB, NIEHS, NIGMS, NINDS, NIA, NIMH, NIDA, OBSSR, ODS) (RFA-TW-03-006)

Microcirculation and Target Organ Damage in Rheumatic and Skin Diseases
(ORWH, NIAMS, NEI) (RFA-AR-03-005)

Pathophysiology and Treatment of Chronic Fatigue Syndrome
(ORWH, ODS, OBSSR, NCCAM, NIAAA, NIAID, NIAMS, NICHD, NHLBI, NIEHS, NINR) (PA-02-034)

Basic Research in the Bladder and Lower Urinary Tract
(ORWH, NIDDK, NIA, NIH) (PA-03-136)

Behavioral, Social, Mental Health, and Substance Abuse Research with Diverse Populations
(ORWH, NIMH, NIDA, NICHD, OBSSR) (PA-01-096)

Women's Health in Sports and Exercise
(ORWH, NIAMS, NICHD) (PA-02-115)

Planning Grants to Organize Programs for International Clinical, Operational, and Health Services Research Training for AIDS and Tuberculosis
(ORWH, FIC, NIAID, NIDA, NIMH, CDC, USAID) (PAR-03-072)

Global Health Research Initiative Program for New Foreign Investigators
(ORWH, FIC, NCI, NHLBI, NEI, NIA, NIBIB, NICHD, NIDA, NIEHS, NIGMS, NIMH, NINDS, OBSSR, ODS) (PAR-03-118)

AIDS International Training and Research Program
(ORWH, FIC, NCI, NHLBI, NIAID, NIDCR, NIMH, NINR, NIAAA, NIDA, OAR) (PA-03-018)

NIH Support for Conferences and Scientific Meetings
(ORWH, NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NCCAM, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NCRR, ODP, OBSSR, ORD, ODS) (PAR-03-176)

TABLE 6

Request for Applications and Program Announcements Sponsored by ORWH, FY 2004

Building Interdisciplinary Research Careers in Women's Health (BIRCWH I)
(ORWH, NIA, NIAAA, NIAID, NIAMS, NCI, NICHD, NCCAM, NIDCD, NIDR, NIDDK, NIDA, NIEHS, NINDS, AHRQ) (RFA-OD-99-008)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH II)
(ORWH, NIA, NIAAA, NIAMS, NICHD, NIDR, NIDDK, NIMH, ODS, AHRQ) (RFA-OD-02-001)

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORS)
(ORWH, NIAMS, NICHD, NIDR, NIDDK, NIDA, NIEHS, NIMH, FDA) (RFA-OD-02-002)

Leiomyomata Uteri: Basic Science and Translational Research
(ORWH, NICHD, NIEHS) (RFA-HD-03-005)

Pharmacogenetics Research Network and Knowledge Base
(ORWH, NIH, NIGMS, NCI, NHLBI, NHGRI, NIDA, NIEHS, NLM) (RFA-GM-4-002)

Interstitial Cystitis/Painful Bladder Syndrome Epidemiology
(ORWH, NIDDK) (RFA-DK-04-009)

Women's Reproductive Health Research Career Development Centers
(ORWH, NICHD) (RFA-HD-03-020)

Phase II International Clinical, Operational, and Health Services Research Training Awards for AIDS and Tuberculosis (Comprehensive ICOHRTA AIDS/TB)
(ORWH, FIC, NIAAA, NIAID, NICHD, NIDA, NIMH, NINDS, CDC, USAID) (RFA-TW-03-003)

Pathobiology of Temporomandibular Joint Disorders
(ORWH, NIDCR, NIAMS) (RFA-DE-03-005)

Global Health Research Initiative Program for New Foreign Investigators
(ORWH, FIC, NCI, NEI, NHLBI, NIBIB, NIEHS, NIGMS, NINDS, NIA, NIMH, NIDA, OBSSR, ODS) (RFA-TW-03-006)

Microcirculation and Target Organ Damage in Rheumatic and Skin Diseases
(ORWH, NIAMS, NEI) (RFA-AR-03-005)

Pathophysiology and Treatment of Chronic Fatigue Syndrome
(ORWH, ODS, OBSSR, NCCAM, NIAAA, NIAID, NIAMS, NICHD, NHLBI, NIEHS, NINR) (PA-02-034)

Basic Research in the Bladder and Lower Urinary Tract
(ORWH, NIDDK, NIA, NIH) (PA-03-136)

NIH Clinical Trial Planning Grant Program
(ORWH, NIH, NIA, NIAAA, NIAMS, NICHD, NCCAM, NIDCD, NIDA, NINDS, OBSSR, ORD, ODS) (PA-04-008)

Supplements to Promote Re-entry into Biomedical and Behavioral Research Careers
(ORWH, NIH, NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NINR, NCCAM, NCRR, FIC, ODS) (PA-04-126)

Behavioral, Social, Mental Health, and Substance Abuse Research with Diverse Populations
(ORWH, NIMH, NIDA, NICHD, OBSSR) (PA-01-096)

Women's Health in Sports and Exercise
(ORWH, NIAMS, NICHD) (PA-02-115)

Planning Grants to Organize Programs for International Clinical, Operational, and Health Services Research Training for AIDS and Tuberculosis
(ORWH, FIC, NIAID, NIDA, NIMH, CDC, USAID) (PAR-03-072)

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TABLE 6 *(continued)*

Request for Applications and Program Announcements Sponsored by ORWH, FY 2004

Global Health Research Initiative Program for New Foreign Investigators
(ORWH, FIC, NCI, NHLBI, NEI, NIA, NIBIB, NICHD, NIDA, NIEHS, NIGMS, NIMH, NINDS, OBSSR, ODS) (PAR-03-118)

AIDS International Training and Research Program
(ORWH, FIC, NCI, NHLBI, NIAID, NIDCR, NIMH, NINR, NIAAA, NIDA, OAR) (PA-03-018)

NIH Support for Conferences and Scientific Meetings
(ORWH, NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NCCAM, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NCRR, ODP, OBSSR, ORD, ODS) (PAR-03-176)

Program grants from this BIRCWH RFA provide institutions in clinical, health, or life sciences or in public health departments, centers, and institutes an opportunity to build a national supply of investigators in women's health research, including research on sex and/or gender differences, as well as research on factors that contribute to disparities in health status or health outcomes for different populations of women.

To date, 24 BIRCWH centers have produced 175 scholars that have gone on to receive NIH awards and academic positions.

Investigators with established research programs covering a broad range of basic and applied biomedical and behavioral science or health services research form an intellectual and technical research base for mentoring IWHR scholars. Mentors from collaborating departments are encouraged to provide needed expertise and resources, as long as the emphasis of IWHR scholars' projects is on research relevant to women's health. Projects are basic, translational, clinical, or health services research, but must be within the biomedical and behavioral purview of NIH and/or the health services research purview of AHRQ. Health services research includes the study of the quality, appropriateness, outcomes, and effectiveness of health care services, as well as the cost, use, and access to health care services.

Trans-NIH Support for BIRCWH I

- National Institute on Aging
- National Institute on Alcohol Abuse and Alcoholism
- National Institute of Allergy and Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Cancer Institute
- National Institute of Child Health and Human Development
- National Institute on Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of Mental Health
- Agency for Healthcare Research and Quality (AHRQ)

Trans-NIH Support for BIRCWH II

- Office of Research on Women's Health
- National Institute on Aging
- National Institute on Alcohol Abuse and Alcoholism

- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Child Health and Human Development
- National Institute of Dental and Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute of Mental Health
- Office of Dietary Supplements
- Agency for Healthcare Research and Quality (AHRQ)

BIRCWH I

ORWH, along with nine NIH institutes and the AHRQ, supports 12 new programs for developing faculty scholars in interdisciplinary women's health research. Sites recruit their own scholars. Those BIRCWH programs are:

Baylor College of Medicine
Houston, Texas
Contact: Haleh Sangi-Haghpeykar, Ph.D.
halehs@bcm.tmc.edu

The Baylor program offers two tracks, molecular/clinical and clinical/health services/population research. Under this framework, 26 mentors from departments of medicine, obstetrics-gynecology, rehabilitation, ethics, molecular medicine, and health services research collaborate to offer an intensive research experience, with a strong focus on molecular and human genetics and cell biology. Where appropriate, scholars will work toward a master's degree, e.g., in public health. Continuing guidance will be provided to scholars after completing the program.

University of Alabama at Birmingham
Birmingham, Alabama
Contact: John Hauth, M.D.
brials@uabmc.edu

A major emphasis of the program at Birmingham is the health problems more common in minority and disadvantaged women. Mentors who work on health disparities were chosen for the program, and scholar candidates with an interest in disadvantaged populations will be particularly sought. Limited experience and advanced tracks feature individualized curricula. Among a total of 24 mentors, seven from obstetrics-gynecology form a subgroup of reproductive health, with 17 others from a diverse group of 11 different departments.

University of California–Los Angeles
Los Angeles, California
Contact: Gautam Chaudhuri, M.D., Ph.D.
gchaudhu@obgyn.medsch.ucla.edu

UCLA offers a highly interactive program involving 32 mentors, representing a mix of basic and clinical research. Areas of interest include developmental biology, molecular genetics, cell biology, behavioral sciences, cardiovascular sciences, cancer, clinical pharmacology, translational and clinical investigation, and health services research. The overall program comprises three phases, with entry depending on the experience level and needs of each scholar.

University of California–San Francisco
San Francisco, California
Contact: Deborah Grady, M.D.
dgrady@itsa.ucsf.edu

UCSF and the Northern California Kaiser Division of Research join forces to focus a program on chronic diseases of women. A core curriculum and tailored course work may be applied toward an advanced degree. Twelve senior mentors plus resource faculty offer a research experience in seven disease areas: cardiovascular, breast cancer, skeletal health, neuropsychiatric disorders, substance abuse, urinary incontinence, and HIV. There are also five cross-cutting research areas: sex hormones, women's imaging, complementary and alternative medicine, health services research, and aging.

University of Connecticut Health Center
Farmington, Connecticut
Contact: Judith Fifield, M.D.
Fifield@nso1.uchc.edu

Twenty-one women's health investigators now scattered across three campuses of the University, including allied health professionals, join as mentors at this site. Areas of research are bone and skeletal biology, addictions and

mental health, reproductive health and sexually transmitted diseases, and gender roles. Basic, clinical, and sociobehavioral approaches will be applied in all these areas. Curriculum and plans are individualized within three tracks: experienced investigator, limited research experience, and degree (M.P.H. or Master of Dental Sciences).

University of Kentucky
Lexington, Kentucky
Contact: Claire Pomeroy, M.D.
cpomer0@pop.uky.edu

The University of Kentucky presents a program organized around three major themes: regulation of menopause and its repercussions for women's health, nutrition-related illnesses and their impact on women, and drug abuse and its relationship to gender (including AIDS/HIV). A didactic phase is tailored to the background and interest of the scholar. There are 18 mentors whose areas of research include cardiovascular, bone, infectious disease, alcoholic liver disease, brain, and aging.

University of Medicine and Dentistry of New Jersey
Newark, New Jersey
Contact: Laura T Goldsmith, Ph.D.
goldsmit@umdnj.edu

The UMDNJ–New Jersey Medical School site provides a strong focus on minority and disadvantaged populations of women. Fourteen mentors offer a research experience on the areas of cardiovascular disease, diabetes, multiple sclerosis, infectious disease, aging, and reproduction and development. Career development includes a core curriculum plus individualized course work, and scholars have the option of working toward a Ph.D. or M.P.H.

University of Michigan
Ann Arbor, Michigan
Contact: Timothy R.B. Johnson, M.D.
trbj@mailgw.obgyn.med.umich.edu

With a focus on gender differences across the life span, 20 mentors at the University of Michigan Medical Center offer research experiences in four target areas: pelvic floor/urology/gynecology (uniting obstetrics-gynecology, urology and nursing research); health services research; reproductive science and women's medicine (including toxicology); and biobehavioral and aging research, especially depression. A Women's Academic Leadership Plan is available as part of a scholar's individualized career plan.

University of North Carolina–Chapel Hill
Chapel Hill, North Carolina
Contact: Bruce Lessey, M.D., Ph.D.
Lessey@med.unc.edu

The University of North Carolina has organized its program around three central themes: biomarkers of therapeutics, prevention and intervention, and health issues of the mature woman. Thirty-six mentors cover a broad array of topics, including cancer, pharmacology, cell biology, nutrition, sexually transmitted diseases, complications of pregnancy, substance abuse, contraception, environment and health, domestic violence, gastroenterology, cancer, cardiovascular disease, and the pelvic floor. Prevention and outcomes research are also featured. Two tracks are available, depending on experience level, and scholars may work toward an advanced degree.

Virginia Commonwealth University
Richmond, Virginia
Contact: Mary Nettleman, M.D.
mnettlem@hsc.vcu.edu

The VCU site focuses on women's health research in five areas: substance abuse, psychiatric genetics, reproductive health, cancer, and diseases associated with aging. Through these areas run themes of basic, clinical, behavioral, epidemiological, and health services research. Individualized course work will prepare scholars for their research experience. The faculty consists of 25 mentors, including a core mentor for each of the areas.

Washington University
St. Louis, Missouri
Contact: Clay Semenkovich, M.D.
Semenkov@im.wustl.edu

Twenty-five mentors provide a newly integrated focus on women's health research across eight focus areas: autoimmune disease, cardiovascular disease, complications of pregnancy, diabetes, obesity and metabolism, osteoporosis, infectious disease, and cancer. Two tracks will serve scholars with substantial or limited

prior research experience. Those with limited experience who are pursuing patient-oriented research will enter the Master of Science in Clinical Investigation Program.

Yale University
New Haven, Connecticut
Contact: Bruce Rounsaville, M.D.
bruce.rounsaville@yale.edu

The Yale program centers on women's health and substance abuse, with 25 mentors from a broad array of basic, clinical, and social science disciplines. Areas are etiology of drug and alcohol abuse in women; the development of new sex-specific treatments; behavioral interventions for drug-abusing mothers and children; sex differences in drug abuse consequences, co-morbidity, particularly stress and depression; and translation of research findings into practice. Clinical scholars have an option of complementing their research with training in substance abuse.

BIRCWH II

Boston Medical Center
Boston, Massachusetts
Contact: Karen Freund, M.D., M.P.H.
karen.freund@bmc.org

Boston University's program addresses the need to increase the number of outstanding investigators trained in clinical research, clinical epidemiology, and health services research. More than 13 mentors are proposed around five major research areas: prevention research, health services outcomes and effectiveness research, addiction medicine, issues of aging women, and the consequences of multiple care giver roles. Scholars enter into one of two pathways, basic (those who have not had formal research training) or advanced research. Scholars also have the option of pursuing a master of science degree in epidemiology.

Brown University
Providence, Rhode Island
Contact: Jeffrey F. Peipert, M.D., M.P.H.
jpeipert@wihri.org

Brown University and its affiliated hospitals present a cross-institutional program organized around five major areas: prevention and behavior change; gender issues in women's health; health services research; HIV/AIDS in women; and obstetric and gynecologic research, including perinatal diagnosis and management, screening in early pregnancy, transitional immunology, and developmental biology and cell dynamics. In addition, there are formal ties with Tugaloo College in Mississippi and links to Xavier University in New Orleans. Scholars have access to 20 mentors that cut across institutions, including Women & Infants Hospital, the George Anderson Outcomes Measurement Unit, and Woods Hole Marine Biological Laboratory.

Duke University
Durham, North Carolina
Contact: Evan R. Myers, M.D., M.P.H.
myers008@mc.duke.edu

Duke University joins forces with North Carolina Central University in designing a program to contribute to improvement in women's health. The research program revolves around four main themes: clinical trials and outcomes; decision-making research; health disparities; and basic and translational research, which includes a wide array of topics, such as the genetics and molecular biology of either breast or ovarian cancer, neuromuscular physiology, and pharmacology of the pelvic floor to the molecular biology of nicotine addiction. More than 25 mentors that cut across disciplines and professions are involved. Two tracks serve scholars with substantial or limited prior research experience. Scholars also have the opportunity of working towards a master's degree in health sciences or clinical research.

Magee-Women's Health Corporation
Pittsburgh, Pennsylvania
Contact: Melissa McNeil, M.D., M.P.H.
mcneilma@msx.upmc.edu

This program is orchestrated through the Magee Women's Research Institute to provide an integrated approach to interdisciplinary research in women's health, focused on four themes that cover women's health from preconception to elderly women: gender-specific developmental biology, women's behavioral health, prevention of adverse reproductive outcomes and chronic diseases, and aging and cancer. Scholars in this program have the

option of working with the 36 mentors whose research areas are encompassed under the umbrella of the four theme leaders.

University of Maryland
Baltimore, Maryland
Contact: Jodi Anne Flaws, Ph.D.
jflaws@epi.umaryland.edu

The University of Maryland presents a program that includes collaboration with Morgan State University and Howard University. Three broad research themes underlie the program: life changes in women's health (including steroid hormone regulation of angiogenesis to the psychometrics of human sexual behavior), adverse conditions and diseases in women (including ovarian hormones and neurological diseases and cancer disparities), and gender differences in pain. Nineteen mentors drawn from the Schools of Dentistry, Medicine, Nursing and Pharmacy are involved. Two tracks are available to selected scholars, depending on a scholar's research background.

SUNY Downstate
Brooklyn, New York
Contact: Alan Gintzler, Ph.D.
alan.gintzler@downstate.edu

Downstate offers a program that links SUNY Downstate Medical Center in research and training collaborations with Kings County Hospital and the Arthur Ashe Urban Health Institute (AAIUH). The program is organized into mentored research areas that reflect the interests of research team mentors. Scholars have opportunities to interact with more than 18 mentors. Six core research areas spanning basic and clinical aspects related to women's health are offered: sex/gender differences in pain and analgesic response, early detection of breast cancer, neurological disorders and epilepsy, diabetes, progression of AIDS using a variety of methodological expertise, and health care disparities and well-being.

Oregon Health & Science University
Portland, Oregon
Contact: Lowell Davis, M.D.
davislo@ohsu.edu

Oregon Health & Science University (OHSU) presents a program based in the School of Medicine, but that draws on the participation of four exceptional OHSU centers, including the Center for Women's Health, Heart Research Center, Oregon Regional Primate Research Center, and the Cancer Institute. Scholars are exposed to 27 mentors, who conduct research in areas of women's health that extend across the life span. The research program builds on a unifying theme of women's health across the life span that is centered around six specific research areas: fetal environments and cardiovascular development, reproduction and health, neurobiology and gender differences, substance abuse, cancer in women, and aging and end-of-life issues.

University of Pennsylvania
Philadelphia, Pennsylvania
Contact: Jerome Strauss M.D., Ph.D.
jfs3@mail.med.upenn.edu

This program, located in the Center for Research for Reproduction and Women's Health at University of Pennsylvania, involves 33 mentors who are organized around six research clusters: brain and behavior, metabolism and aging, cell and tissue homeostasis, hormones, reproduction and urologic function, infection and immunity, and cardiac and pulmonary. The program offers the possibility of enrollment in a master's or doctoral program. Scholars begin with a period of mentored research training prior to transition into independent research with faculty appointment.

Stanford University
Stanford, California
Contact: Marcia Stefanick, Ph.D.
stefanick@stanford.edu

Stanford University offers mentoring in women's health research from bench to bedside, from basic to clinical research. The program features more than 23 mentors from a variety of disciplines encompassing 12 major research areas under basic and clinical research divisions, including midlife aging/cardiovascular disease, adolescent health, medical information technology, medicine/CV/diabetes, cancer, reproductive/urogenital health, genetics, cancer biology, and tissue engineering. Scholars will have two pathways available, basic and clinical research.

Tulane University
New Orleans, Louisiana
Contact: Jeanette H. Magnus, M.D., Ph.D.
jmagnus@tulane.edu

Tulane, in partnership with Xavier University, offers a program with a strong focus on patient-oriented research related to cardiovascular health, particularly among African American women. Scholars have access to 15 mentors with a broad range of basic, biomedical, behavioral, and health services research experience across the schools of Tulane and Xavier University. The areas of research focus on two highly underresearched areas in women's health—cardiovascular disease and hypertension—with the ultimate goal of training scientists to address sex/gender and disparities issues in cardiovascular health.

University of Utah
Salt Lake City, Utah
Contact: Leigh A. Neumayer, M.D.
Leigh.neumayer@hsc.utah.edu

The University of Utah presents a program that represents a collaboration of the Colleges of Health, Nursing, Pharmacy, and Medicine. The program involves 17 mentors from various disciplines. Four principal areas of research emphasis are offered to scholars: aging disorders, cardiovascular disorders, cognitive/neurological disorders, and oncologic disorders. Selected scholars are afforded the choice of two levels, entry (limited research experience) and advanced (significant prior research experience). Scholars also have the option of pursuing an innovative program leading to a master of science degree.

Vanderbilt University
Nashville, Tennessee
Contact: Stephen Entman, M.D.
stephen.entman@vanderbilt.edu

This program represents a partnership between Vanderbilt University and Meharry Medical College. The research program is designed around six interdisciplinary research themes: cancer/neoplasia, cardiovascular/diabetes, clinical pharmacology, neurosciences/behavioral health, endometrial biology/reproductive toxicology, and health services/outcomes research. Selected scholars have the opportunity to interact with 25 mentors from a variety of departments/schools, including the school of medicine, clinical departments, preventive medicine, psychiatry and the Institute for Public Policy Studies.

Scholar areas of research interest include: mental health, diabetes, cardiovascular health, arthritis/musculoskeletal health, neurological disorders, menopausal hormone therapy, and sex/gender differences in substance abuse and HIV therapies.

Since 2000, a total of 177 scholars have trained under the BIRCWH I and II programs; 49 have completed the program and 115 scholars are currently enrolled. Of these scholars, 72 percent were female and 28 percent were male; 10 percent were underrepresented minorities; and 49 percent had medical degrees, 36 percent had doctoral degrees, 10 percent held both medical and doctoral degrees, and 5 percent held other health professional degrees.

The scholars have published 634 publications and 526 abstracts, and received 40 NIH grants. The NIH grants are from a variety of NIH ICs, including NIDDK, NICHD, NIAMS, NIA, and NHLBI. Other PHS grants include one scholar who was named Director of the Center of Excellence in Women's Health at Brown University and one scholar who received an R03 from AHRQ. The scholars have also received more than 70 awards from industry and institutional sources.

Examples of selected topics include:

Mental Health

- Assessing the impact of SSRI antidepressants on popular notion of women's depressive illness
- Sexual harassment and psychological health of women
- Emergency department screening and treatment intervention to improve he safety and health of battered women
- Examining communication and power dynamics of female patients and their health care providers
- Role of maternal depression on women's breastfeeding decisions

Diabetes

- Ethnic differences in insulin insensitivity and B cell function
- Knowledge of risk for heart disease among people with diabetes: relations to gender, ethnicity and diabetes treatment regimen
- Mechanism by which diabetes contributes to CVD

Cardiovascular Health

- Ceramide in circulating lipoprotein and vascular-endothelium
- Estrogen and angiogenesis
- Coronary heart disease risk in women with spinal cord dysfunction
- Primary and Secondary Prevention – cardiovascular disease associated with mental health risk factors
- Cardiovascular disease and chronic kidney disease (determine the modifiable environmental risk factors and genetic risk determinants for CVD)
- Study of the properties of a single item global health measure for predicting patient outcomes and high-risk CVD
- Vascular disease in Women

Arthritis/Musculoskeletal Health

- Utilization of services and patterns of specialty care for women with rheumatoid arthritis
- Exercise, amenorrhea, stress, and bone health
- A role for activated T lymphocytes in the bone loss associated with Crohn's disease
- Pharmacogenetics of methotrexate toxicity and efficacy in rheumatoid arthritis

Neurological Disorders

- Gender susceptibility to neurological dysfunctions by altering GABA receptor signaling
- Effect of gender and phenotype in a subset of disorders: neurotransmitter deficiency-related disorders
- Hormone changes induced by seizure activity in rats

Menopausal Hormone Therapy

- Estrogen and angiogenesis
- Effects of estrogen on cardiac fibrosis after MI
- HRT and effects on cognition

Sex/Gender

- Sex differences in substance abuse
- Importance of gender and social supports in the nursing home settign
- Sex differences in HIV therapies

Substance Use

- Sex differences in the etiology of substance abuse
- Gender-specific pathways linking stress and cocaine relapse
- Sex differences in vulnerability to cocaine addiction
- Smoking cessation rates for women with abnormal PAPs

Reproductive Health

- Risk factors for sexually transmitted infections among women in an Alabama HIV clinic
- Increased vaginal levels of a marker of collagen synthesis and preterm birth
- Epidural-related fever and maternal serum interleukin-6 levels
- Synchrony between LH and leptin pulsatile secretion in women with polycystic ovary syndrome
- Mouse models of premature ovarian failure

- Innovative approach to childbirth decision-making using mathematical model
- NK cell gene expression in normal pregnancy vs. recurrent spontaneous miscarriage
- Insulin sensitivity and pregnancy-related weight gain
- Development of a decision aid for patients considering treatment for endometriosis pain

Cancer Research

- Identifying low-penetrance breast cancer susceptibility genes
- Quantifying breast composition for breast cancer risk using X-ray absorptiometry
- Ovarian cancer: immunogenic vs. non-immunogenic profiles
- Causes and consequences of genetic instability in ovarian cancer
- Breast cancer – mechanisms of ischemia, reperfusion injury, and ischemic preconditioning
- Universal breast cancer antigens as targets linking early detection and therapeutic vaccination

Molecular Biology/Genetics

- Genetics of endometriosis (using microarrays)
- Genetics of breast cancer

Health Services/Disparities

- Hypertension in African American women and the effects of exercise
- Health services in HIV-infected incarcerated women
- Improving health outcomes for women with chronic illness
- Effect of risk perception on breast cancer and colorectal cancer screening
- Social and cultureal factors of significance in managing chronic diseases in Caribbean immigrants

Molecular Biology/Genetics

- Genetics of endometriosis (using microarrays)
- Genetics of breast cancer

Trauma

- Estrogen and prolactin in septic shock
- Research independence
- Global metric beyond individual achievement looking at how much collaborative research is generated by the BIRCWH centers
- Assessment of scholars based on their individual baseline level when they entered the program as they are a diverse group of researchers
- Percentage of scholars who continue to conduct research in women's health post-BIRCWH
- Publications: high- vs. low-impact journals
- Number of grants submitted per scholar compared to the number funded
- Percentage who go into academia
- Number of scholars teaching clinical research methods (recognition for teaching)
- Number publications, positions held, awards, honors, and oral presentations

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health

ORWH funded 11 Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) in FY 2002. Funding for the centers is approximately $11 million per year for 5 years with co-funding by NIAMS, NICHD, NIDDK, NIDA, NIMH, NIEHS, and the FDA. These

centers provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. The SCOR program complements other federally supported programs addressing women's health issues. Such programs include: the Building Interdisciplinary Research Careers in Women's Health (BIRCWH), the Women's Reproductive Health Research Career Development Centers (WRHR), and numerous NIH RFAs and PAs.

Each SCOR promotes interdisciplinary collaborations and the development of a research agenda bridging basic and clinical research on sex and gender factors underlying a priority health issue. Research priority areas addressed by the new centers, include mental health, reproductive health, pain disorders, and urinary tract health. The following section outlines SCOR themes, center directors, individual projects, and affiliations.

Emory University
Pharmacology of Anti-epileptic and Psychotropic Medications during Pregnancy and Lactation
Zachary Stowe, M.D.

Models will be developed for the pharmacology of anti-epileptic and psychotropic drugs during pregnancy and lactation. This information will help physicians provide risk–benefit information to pregnant and lactating women.

Medical University of South Carolina
Role of Sex and Gender Differences in Substance Abuse Relapse
Kathleen Brady, M.D., Ph.D.

The role of sex and gender differences in substance abuse relapse will be studied, with particular emphasis on elucidating factors contributing to relapse. Tobacco, cocaine, and alcohol will be studied.

Northwestern University
Genes, Androgens, and Intrauterine Environment in Polycystic Ovarian Syndrome
Andrea Dunaif, M.D.

Genes, androgens, and the intrauterine environment in polycystic ovarian syndrome (PCOS) provide the theme for studies elucidating the pathogenesis of PCOS.

University of California–Los Angeles
Sex and Gender Factors in the Pathophysiology of Irritable Bowel Syndrome and Interstitial Cystitis
Emeran Mayer, M.D.

Sex and gender factors underlying the pathophysiology of irritable bowel syndrome and interstitial cystitis will be evaluated.

University of California–San Francisco
Mechanisms Underlying Female Urinary Incontinence
Jeanette Brown, M.D.

Mechanisms underlying female urinary incontinence will be studied using epidemiologic, biologic, and molecular approaches. The impact of diabetes on urinary incontinence will be evaluated.

University of Maryland
Sex Differences in Pain Sensitivity
Joel Greenspan, Ph.D.

The research goals include an understanding of neuronal mechanisms underlying sex differences in pain sensitivity, in particular for visceral and temporomandibular pain.

University of Michigan–Ann Arbor
Birth, Muscle Injury, and Pelvic Floor Dysfunction
John, DeLancey, M.D.

Studies will focus on understanding an important clinical issue for women, stress incontinence, and more specifically the effects of childbirth on the development of urinary incontinence.

University of Pittsburgh
Genetic and Environmental Origins of Adverse Pregnancy Outcomes
Gerald Schatten, Ph.D.

Genetic and environmental factors contributing to adverse pregnancy outcomes will be sought, particularly for recurrent pregnancy loss.

University of Washington
Mechanisms by Which Drug Transporters Alter Maternal and Fetal Drug Exposure during Pregnancy
Jashvant Unadkat, Ph.D.

Mechanisms by which drugs are transported in the body control maternal and fetal drug

exposure during pregnancy. Alterations in drug transport during pregnancy are being studied. Data should allow predictions on the magnitude of change in exposure likely to be observed when drugs are administered to pregnant women.

Washington University
Molecular and Epidemiologic Basis of Acute and Recurrent Urinary Tract Infections in Women
Scott Hultgren, Ph.D.

The molecular and epidemiologic basis of acute and recurrent urinary tract infections (UTIs) in women are being studied. UTIs are among the most common infectious diseases in the United States, and primarily affect women.

Yale University
Sex, Stress, and Cocaine Addiction
Rajita Sinha, Ph.D.

Sex, stress, and cocaine addiction are the core of a multidisciplinary program leading to sex-specific prevention and treatments.

Interdisciplinary Symposium

In FY 2004, ORWH lead the development of the first Interdisciplinary Symposium on Research on Women's Health and brought together BIRCWH I and II PIs, BIRCWH scholars, and PIs from the SCOR program. Meeting objectives were:

- To increase knowledge of collaborative and interdisciplinary research activities in women's health
- To increase understanding of sex and gender differences that contribute to biological differences in cellular tissue organ responses between men and women or conditions that have enhanced clinical presentation in women
- To increase understanding of the effects of gender on psychological, social, and behavioral determinants of health and disease.

This program will become an annual event.

ORWH established an External Advisory Committee (EAC) to review SCOR programs and provide guidance to the office. Dr. Vivian Pinn selected members of the CCRWH and ACRWH to review SCOR programs. The nine-member committee noted that the SCORs have begun to demonstrate success in meeting their scientific objectives, and have proven successful in mobilizing scientists of diverse disciplines to bring their scientific expertise to bear on examining how sex and gender factors contribute to health and disease. Significant progress has been demonstrated in each center, including development of experimental methodology, implementation and expansion of research, and recruitment of clinical participants. SCOR investigators are actively promoting sex and gender research institutionally through pilot projects, seminars, and training junior investigators. These investigators have also taken the initiative to embark upon collaborations with other SCORs.

Chronic Fatigue Syndrome

In view of its long history in collaborative, trans-NIH efforts, ORWH was given responsibility to coordinate the NIH Chronic Fatigue Syndrome (CFS) Program in FY 2002. Its mission was to establish an interdisciplinary approach to this complex disorder that would allow each IC represented to contribute it's expertise to creating research initiatives that would be more effective in achieving answers to the dilemma faced by people with CFS and other chronic, multisystemic illnesses of unknown origin. This dilemma becomes more important as the population ages and the model of disease shifts from acute to chronic and multifaceted conditions.

CFS is a debilitating and complex syndrome that may involve multiple bodily symptoms and is characterized by profound fatigue, which is not alleviated by bed rest and can be exacerbated by physical or mental activity. People with CFS often function at substantially lower levels of activity from their pre-onset capacities. Neither a specific cause, diagnostic test, nor treatment has been identified for this illness. It is possible that multiple subcategories of conditions are subsumed under this rubric. Approximately

1 percent of the U.S. population is affected. While it appears that Caucasian women suffer with CFS more frequently than do men or women from other ethnic groups, epidemiologic studies funded by ORWH indicate that this gap may be narrowing. Also important is that 80 percent of people identified in such studies have not been diagnosed or treated. There is also a substantial pediatric population with this condition. CFS represents a significant public health problem that is estimated by the Centers for Disease Control and Prevention (CDC) to have an economic burden of $9.1 billion.

ORWH is the NIH representative on the DHHS Chronic Fatigue Syndrome Advisory Committee (CFSAC). In addition, ORWH is responsible for coordinating NIH CFS research activities in order to stimulate interdisciplinary research in this area. This is accomplished through an *Ad Hoc* Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG), which was convened and is chaired by ORWH staff. The CFSWG is comprised of members from 16 different NIH ICs, including NIAID, NINDS, NHLBI, NIAMS, NIMH, NICHD, and NCRR (Appendix E).

In June 2003, ORWH sponsored a scientific workshop for research on CFS, "Neuro-Immune Mechanisms and Chronic Fatigue Syndrome: Will understanding central-mechanisms enhance the search for the causes, consequences and treatment of CFS?" The purpose of the workshop was twofold: to interest the intramural scientific community in CFS research, and to form the basis for future ORWH–CFSWG activities. The recommendations from the workshop illuminated the understanding of how the brain, as the mediator of the various body systems involved, fits into the schema for understanding CFS. The proceedings from this workshop were published in FY 2004 (NIH Publication 04-5497). A new PA, which will update PA-02-034 and include these recommendations, will be released in FY 2005. The Request for Applications (RFA) based on the findings from this scientific workshop will be issued later in 2005.

As a result of intramural interest generated at this workshop, ORWH and a NINDS intramural scientist, Dr. David Goldstein, were instrumental in forming a new, multi-institute, intramural scientific interest group (SIG). ORWH sponsored the charter meeting of the SIG on Scientific Integrated Medicine in April 2004. In addition, ORWH established and expanded the CFSWG page on its website to include more scientific materials for researchers. The CFSWG is considering and reviewing the many models available for stimulating clinical research in CFS. In the coming year, NIH will continue to explore and implement science-driven initiatives to advance knowledge of CFS.

ORWH-SPONSORED RESEARCH PLANNING AND DEVELOPMENT CONFERENCES

During FY 2003 and 2004, ORWH co-funded a number of conferences and workshops with NIH ICs, as well as other Federal agencies. The detailed information for these conferences is contained in Appendix H.

In FY 2003, ORWH took the lead in convening three conferences: *Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance; Neuroimmune Mechanisms and Chronic Fatigue Syndrome;* and *Lupus Today: Research Into Action*. Brief summaries are in this section.

Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance

ORWH and the Recruitment, Retention, and Integrity in Clinical Studies Task Force convened a meeting on January 6-9, 2003 called *Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance*.

At the opening session, participants discussed the critical role of inclusion in increasing knowledge about the contributions of sex differences and/or similarities to the health and disorders of women and men and minorities. Lessons learned to date concerning the recruitment and retention of women and other participants from

clinical prevention and treatment trials, as well as longitudinal cohort studies, conducted over the past decade were examined. During the course of this 4-day meeting, participants identified and discussed the challenges that continue to confront researchers as they endeavor to recruit and retain women, minorities, and other participants in clinical research to ensure that study populations are representative, relevant, and appropriate for addressing scientific questions important to the public health.

Workshop participants also considered carefully and at length the emerging ethical and policy issues that present both challenges and opportunities for women's health research and studies that will elucidate sex and gender factors in health and disease.

The full summary may be found at: *http://orwh.od.nih.gov/pubs/SMR_Final.pdf*. Published proceedings (NIH Publication No. 03-5403) may be ordered at *http://137.187.172.239/request_pub3.asp*.

Neuroimmune Mechanisms and Chronic Fatigue Syndrome

A scientific workshop sponsored by the ORWH and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome was held on June 12-13, 2003.

This scientific research workshop was convened in order to stimulate interdisciplinary interest in studying CFS. It is the first in a series and was focused on exploring the following questions:

- Can CFS and related disorders be understood as disorders of central nervous system physiology?
- If CFS is a disorder of the central nervous system (CNS), what methodologies are available to investigate such disorders?
- Are there therapeutic approaches that target CNS physiology that should be applied to CFS?

The CNS was chosen as the main focus not only because many symptoms of CFS can be understood in terms of CNS function, but also because the brain is the organ that controls and regulates all action and interaction between the diverse body systems affected in CFS. Also, the input from the external environment could prove to be the integrative model in which to search for the causes, consequences and treatments of CFS.

The full summary may be found at: *http://orwh.od.nih.gov/pubs/cfs_june03report.pdf* Published proceedings (NIH Publication No. 04-5497) may be ordered at *http://137.187.172.239/request_pub3.asp*.

Lupus Today: Research Into Action

A scientific conference on the current status and future directions of research and treatment for systemic lupus erythematosus (SLE or lupus) was held on September 5-6, 2003.

Lead conveners for the Lupus Today conference were:

- Office of Research on Women's Health, NIH, DHHS
- Office on Women's Health, OS, DHHS
- National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, DHHS

Federal co-sponsors for the conference were:

- National Center on Minority Health and Health Disparities, NIH, DHHS
- National Center for Research Resources, NIH, DHHS
- National Heart, Lung, and Blood Institute, NIH, DHHS
- National Institute of Allergy and Infectious Diseases, NIH, DHHS
- National Institute of Diabetes and Digestive and Kidney Diseases, NIH, DHHS
- National Institute of Environmental Health Sciences, NIH, DHHS
- National Institute of Neurological Disorders and Stroke, NIH, DHHS
- Office of Women's Health, CDC, DHHS

- Office of Women's Health, FDA, DHHS
- Health Resources and Services Administration, DHHS
- Office of Minority Health, OS, DHHS

Advocacy co-sponsors were:

- Alliance for Lupus Research
- American Autoimmune Related Diseases Association
- Arthritis Foundation
- Lupus Clinical Trials Consortium, Inc.
- Lupus Foundation of America
- Lupus Research Institute
- Rheuminations, Inc.
- S.L.E. Foundation, Inc.

This conference highlighted key research accomplishments and what they may represent for the current and future management of lupus. National leaders in lupus research discussed the latest scientific discoveries that are opening up new avenues for diagnosis and treatment. The session discussed how lupus affects patients of different ages and populations, current clinical diagnostics, and treatments used today in lupus, including emerging technologies and how they are being applied to the development of new diagnostic tools for lupus. Speakers also presented cutting edge research on the basic mechanisms of the disease and how the new information may translate into new treatments.

In addition, there was a panel discussion on patient participation in lupus studies and how patients and patient advocacy organizations view lupus research today. This session consisted of a panel discussion on the challenges patients face today and how they cope. The panelists also looked at the role of advocacy groups and the information available on patient participation and patient rights and protections in clinical trials.

Another panel focused on current and future lupus clinical trial opportunities and barriers from both the private and public health perspectives. Each will include a basic overview of the disease mechanisms on which the intervention is thought to work and the outcomes to be measured. This session will focus on a panel presentation and discussion of the opportunities for new trials, and discussion of obstacles and possible solutions for expanding current clinical trials in SLE.

The goal of this conference was to inform, energize, and share the excitement about the future of lupus research with patients and their families, physicians, health care workers, scientists, and organizations that support lupus research and outreach. The executive summary may be found at: *http://orwh.od.nih.gov/news/lupustoday.pdf*. A videotape of the entire conference may be viewed online at:

- Day 1: *http://videocast.nih.gov/ram/lupus090503.ram*
- Day 2: *http://videocast.nih.gov/ram/lupus090603.ram*

MONITORING ADHERENCE TO THE NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH

Historical Background

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by NIH has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985, NIH established a policy in 1986 for the inclusion of women in clinical research. This policy, which *urged* the inclusion of women, was first published in the *NIH Guide to Grants and Contracts* in 1987. Later that year, minority and other scientists at NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the *NIH Guide*, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In July 1989, an NIH Memorandum on Inclusion stated that research solicitations should encourage inclusion of women and minorities and require a rationale if excluded,

and that executive secretaries of scientific review groups should ensure that responsiveness to policy would be addressed and indicated in summary statements. In 1990, the Congressional Caucus for Women's Issues requested the U.S. General Accounting Office (GAO) to conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, in Congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow, not well communicated, that gender analysis was not implemented, and that the impact of this policy could not be determined. The GAO testimony also indicated that there were differences in the implementation of the policy recommending the inclusion of minorities, and that not all institutes and centers factored adherence to these policies into the scientific merit review.

In order to ensure that the policies for inclusion were firmly implemented by NIH, Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (PL 103-43),[5] entitled Women and Minorities as Subjects in Clinical Research. In 1994, NIH revised its inclusion policy to meet this mandate that women and minorities must be included in all of its clinical research studies. The Revitalization Act essentially reinforced the existing NIH policies, but with four major differences:

- that NIH ensure that women and minorities and their subpopulations be included in all clinical research;
- that women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;
- that cost is not allowed as an acceptable reason for excluding these groups; and,
- that NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies

Revised inclusion guidelines developed in response to this law were published in the *Federal Register*[6] in March 1994, and became effective in September 1994. The result was that NIH could not and would not fund any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in fiscal year 1995 and thereafter that did not comply with this policy. NIH's administrative procedures allow consideration of applications through a peer-review sytem. During initial peer review, the Scientific Review Group (SRG) evaluates the proposed enrollment of each project involving human subjects and determines whether the plan to include women and minority subjects is scientifically acceptable. The implementation plan determines that an application may be unacceptable if it: 1) fails to provide sufficient information about target enrollment; 2) does not adequately justify limited or lack of inclusion of women or minorities; or 3) does not realistically address recruitment and retention. For NIH-defined Phase III clinical trials, the SRG also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic groups. Applications with unacceptable inclusion plans receive an unacceptable gender or minority code, resulting in a bar-to-funding. Such clinical research studies cannot be funded until NIH staff is assured of compliance from the investigators. This may involve changes related to study design. Sometimes applicants are able to remedy the deficiencies found during initial review by providing additional information about the intended enrollment demographics. Research awards covered by this policy require the grantee to report annually on enrollment of women and men, and on the race and ethnicity of research participants so that accrual can be monitored. Annual progress reports submitted by the grantee contain information on research progress that include research participant enrollment, retention, and, when available, preliminary and/or final analyses, including analyses by sex/gender and race/ethnicity.

Strategies to ensure uniform implementation of the revised guidelines across NIH were developed through the establishment and

[5] Public Law 103-43. National Institutes of Health Revitalization Act of 1993. 42 USC 289 (a)(1).
[6] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508 (1994).

deliberations of an NIH Tracking and Inclusion Committee made up of representatives of the directors of each of the ICs (Appendix F). This trans-NIH committee, convened by ORWH and co-chaired with a senior IC official, meets on a regular basis, focusing on consistent and widespread adherence to the NIH guidelines by all the ICs. Working in collaboration with the Office of Extramural Research, the Office of Intramural Research, and other components of NIH, ORWH coordinates the activity of developing and establishing data collection and reporting methodologies to ensure uniform standards and definitions in the reporting of data on women and minority participants in NIH-funded clinical research.

To ensure NIH-wide adherence to the revised inclusion guidelines, in 1994 NIH conducted extensive training on the revised inclusion guidelines for more than 1,000 NIH staff members with review, program, grants management, and/or contract management responsibilities. Additionally, four publications were distributed to further reinforce adherence to the revised inclusion guidelines.[7-10] NIH staff, in turn, clarified the requirements to applicants, reviewers, and other members of the research community. NIH staff members, reviewers, and applicants received written guidance about the requirements that outlined, in great detail, the circumstances under which it may be acceptable to use study populations deficient in women or minority participants, pointing out that the justification must be compelling and the scientific objectives of the research must be maintained. Training was especially important in light of the 1990 GAO findings that an earlier policy was inconsistently applied and had not been well communicated or understood within NIH or in the research community.

A variety of outreach activities were initiated to explain the revised policy to the scientific research community and to clear up common misunderstandings about the new requirments. Recognizing the importance of both recruitment and retention of human subject volunteers, NIH issued several articles[11-12] and an outreach notebook entitled *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*, that outlines elements of outreach processes, offers practical suggestions, and provides references to additional sources of information. The outreach notebook is available on the ORWH's website at *http://orwh.od.nih.gov/pubs/outreach.pdf*. It also includes the full text of the 1994 implementation guidelines, as well as a questions-and-answers document to provide more detailed policy guidance and answers to some of the more commonly asked questions. ORWH also has available a full report of its workshop on *Recruitment and Retention of Women in Clinical Studies*.

In June 1994, ORWH convened a meeting of Institutional Review Board (IRB) chairs to discuss their role in implementing the revised policy. In 1996, ORWH reconvened these IRB chairs, along with representative members of the ORWH Recruitment and Retention Task Force, other experts, and representatives from NIH ICs, to discuss their experiences in implementing the 1994 guidelines. In these meetings, investigators expressed a number of lingering concerns, most notably whether it was realistic for the law to declare that cost is not a factor in designing clinical studies. Participants also raised questions about inclusion of women of childbearing potential, liability in clinical trials, and barriers to the recruitment of minority subjects. Other participants, however, noted that their worst fears about the 1994 guidelines did not materialize, in part because NIH focused on scientific considerations when developing its policy. They reported improved collaboration among institutions and emphasized the continued need for better outreach and for sharing information about effective recruitment strategies. Many noted the importance of considering community concerns,

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[7] Hayunga, E.G.,Costello, M. D. Pinn, V. W., Demographics of Study Populations, *Applied Clinical Trials*, Vol. 6, No. 1, p. 41-45, 1997.

[8] Hayunga, E. G. and Pinn V. W., Implementing the 1994 NIH Guidelines, *Applied Clinical Trials*, Vol. 5, No. 10, p. 34-40, 1996.

[9] Hayunga, E. G. and Pinn V. W., NIH Response to Researchers' Concerns, *Applied Clinical Trials*, Vol. 5, No. 11, p. 59-64, 1996.

[10] LaRosa, J. H., Seto, B., Caban, C. E., Hayunga, E. G., Including Women and Minorities in Clinical Research, *Applied Clinical Trials*, Vol. 4, No. 5, p. 31-38, 1995.

[11] McCarthy, C. R., Historical Background of Clinical Trials Involving Women and Minorities, *Academic Medicine*, Vol. 69, No. 9, p. 695-698, 1994.

[12] Pinn, V. W., The Role of the NIH's Office of Research on Women's Health, *Academic Medicine*, Vol. 69, No. 9, p. 698-702, 1994.

particularly those of minority populations who may feel that they are not included in enough research studies or who do not receive research results after participating in studies.

Continuing Implementation and Monitoring Activities: 2000 to the Present

Following a Congressional request for an assessment of NIH's progress in implementing the1994 guidelines on including women in clinical research, the GAO issued another report in May, 2000, entitled *Women's Health—NIH Has Increased Its Efforts to Include Women in Research*.[11] It concluded that in the past decade, NIH has made significant progress in implementing a strengthened policy on including women in clinical research and highlighted several examples:

- NIH issued guidelines to implement the 1993 NIH Revitalization Act and conducted extensive training for scientists and reviewers;
- the review process for extramural research treats the inclusion of women and minorities as a matter of scientific merit, affecting a proposal's eligibility for funding;
- the intramural research program now implements the inclusion policy;
- NIH maintains a centralized inclusion tracking data system that serves as a tool for monitoring the implementation of the inclusion policy; and
- in FY 1997, more that 62 percent of participants in NIH-funded clinical research studies were women. Minority women were also well represented. However, the proportion of Hispanic women enrolled was below their proportion in the general population.

The GAO report also included two specific recommendations to the Director of NIH to ensure the following:

- that the requirement be implemented that Phase III clinical trials be designed and carried out to allow for the valid analysis of differences between women and men, and communicate this requirement to applicants as well as requiring peer review groups to determine whether each proposed Phase III clinical trial is required to have such a study design, and that summary statements document the decision of the initial reviewers; and
- that the NIH staff who transmit data to the inclusion tracking data system receive ongoing training on the requirements and purpose of the system.

Immediately following the release of this report, an NIH Subcommittee Reviewing Inclusion Issues was formed, consisting of representatives from several ICs, ORWH, OER, and OIR, to re-examine NIH's system for tracking data on the inclusion of women and minorities in clinical research, recommend any necessary changes to improve its accuracy and performance, and reiterate the NIH policy. Several actions resulted to clarify the requirement for NIH-defined Phase III clinical trials to include women and minority groups, if scientifically appropriate, and for analysis of sex/gender and/or racial/ethnic differences to be planned and conducted by investigators engaged in NIH-funded research. These included:

- In October 2001, the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research and Amended Notice to the *Guide for Grants and Contracts* were updated and posted on the Internet with links to the ORWH home page and NIH web page at: *http://grants1.nih.gov/grants/funding/women_min/women_min.htm*. These documents supercede the 1994 *Federal Register* notice (*http://grants.nih.gov/grants/guide/notice-files/not94-100.html*) and the August 2000 notice in the *NIH Guide to Grants and Contracts* (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html*). These updated versions incorporate the definition of clinical research as reported in the 1997 Report of the NIH Director's Panel on Clinical Research and the Office of Management and Budget (OMB) Directive

[13] Women's Health: NIH Has Increased Its Efforts to Include Women in Research (GAO/HEHS-00-96, May, 2000).

15 racial and ethnic categories to be used when reporting population data. They also provide additional guidance on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials.

- The 1997 Report of the NIH Director's Panel on Clinical research defined clinical research as: 1) Patient-oriented research. Research conducted with human subjects (or on material of human origin, such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; 2) Epidemiologic and behavioral studies; and 3) Outcomes research and health services research. The report may be found at *http://www.nih.gov/news/crp/97report/execsum.htm*.

- The 1997 Office of Management and Budget (OMB) Directive 15 minimum standards for maintaining, collecting and reporting data on race and ethnicity were incorporated into the updated *Guide Notice for Grants and Contracts*. The primary differences from the previous categories were: 1) the Hispanic population is considered an ethnicity and reported separately from racial data; 2) there is a separate racial category for Asian population data and Hawaiian and Pacific Islander population data; and 3) respondents are given the option of selecting more than one race. (See Appendix E)

- An *NIH Guide Notice* was posted on the Internet with a link to the web page, Inclusion of Women and Minorities Policy Implementation at: *http://grants1.nih.gov/grants/funding/women_min/women_min.htm*. This restated that NIH-defined Phase III clinical trials must be designed and conducted in a manner sufficient to allow for a valid analysis of whether the variables being studied affect women or members of minority groups differently than other subjects.

- A new term and condition of award statement was developed and applied to awards made after October 1, 2000 that have NIH-defined Phase III clinical trials. This statement indicates that a description of plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups must be included in clinical trial protocols and the results of subset analyses must be reported to NIH in Progress Reports, Competitive Renewal Applications (or Contract Renewals/Extensions), and in the required Final Progress Report.

- Effective October 1, 2000, language was incorporated in the NIH solicitations for grant applications and contract proposals (Program Announcements [PAs], Request for Applications [RFAs], and Request for Proposals [RFPs]) that stated the requirements for NIH-defined Phase III clinical trials clarifying the requirements that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable, and b) all investigators must report accrual, and conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

- In April 2001, guidelines and instructions for reviewers and Scientific Review Administrators were developed to emphasize and clarify the need to review research proposals that are classified as NIH-defined Phase III clinical trials for both inclusion requirements and issues related to analyses by sex/gender and/or race/ethnicity. Instructions were developed for the proper documentation to include in summary statements to address adherence to these policies.

- Following completion of the updated guidelines and instructions, training to ensure compliance with this policy was provided to NIH program and review officials, grants and contracts management staff, and current and prospective research investigators. Several training initiatives were implemented:
  - As part of an NIH Symposium: Human Subjects Update, the revised policy on inclusion of women and minorities and the revised NIH Instructions to Reviewers Guidelines for Evaluating the Inclusion of Women and Minorities as Subjects in Clinical Research were used as the basis for a required training session for NIH staff. An extramural portal has been created on the NIH home page to inform investigators about all of the regulations, policies and guidance with regard to human subjects. This url is: *http://grants1.nih.gov/grants/policy/hs/index.htm*.
  - An additional training session regarding a Grants Policy Update: Humans and Animals was held in December, 2000 where several hundred additional extramural and intramural researchers were trained. An extramural portal has been created on the NIH home page to inform investigators about all of the regulations, policies and guidance with regard to human subjects. This url is: *http://grants1.nih.gov/grants/policy/hs/index.htm*.
  - Additional training sessions were held for all NIH program and grants management staff.
- The PHS 398 Grant Application was significantly revised to provide additional instructions about the Women and Minorities Inclusion Policy and the revised form will be mandatory beginning May 10, 2005.
- A videocast training session was held on Sex/Gender and Minority Inclusion in Clinical Research. This session was developed for all program, grants management, review and contract staff who administer clinical research and provided information on the updated policies and procedures on sex/gender and minority inclusion. A comprehensive training manual explaining the new policies and procedures was developed as a training resource. The training session and manual is electronically available for all NIH staff.
- Reviewers are instructed about the policy through instructions provided with review materials as well as by orientation from the Scientific Review Administrator at the beginning of each SRG meeting. Additionally, a training session, Inclusion of Children, Women, and Minorities: What SRA's and Reviewers Need to Know!, was held for the Center for Scientific Review and highlighted the requirements and issues for scientific review staff.
- The Clinical Center now has available a web-based educational module for the comprehensive training programs for intramural and other research investigators. All principal investigators are required to complete the Clinical Research Training Course for Intramural Investigators or equivalent prior to implementing a protocol and consideration is being given to making this a requirement for all investigators.
- In 2003, ORWH sponsored a workshop, *Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance*. This workshop discussed lessons learned, continuing challenges, and emerging ethical and policy issues concerning the recruitment and retention of women and other participants in clinical studies during the past decade.

The Office of Extramural Research has made available existing training materials on the population tracking system website on the NIH Intranet. Information includes: the training workbook, Sex/Gender and Minority Inclusion in Clinical Research, a series of quick tips and case examples, as well as the help section of the population tracking module itself. A training subcommittee of the full NIH Tracking and Inclusion Committee

has been established to develop new training documents and methods of training for NIH staff and the extramural research community.

Major changes have been made to the population tracking system to help NIH staff in monitoring compliance with the NIH inclusion policy. For example, the Population Tracking Grant Snapshot report was revised to provide easy access for NIH staff to the population data. Additionally, several population inclusion reports were added to the NIH Query View Report system, thus providing broader access to the data. As well, user roles were revised and expanded to all the Division of Extramural Activities support staff to assist in the data entry functions.

Communication and Outreach Efforts to the Scientific Community

Outreach efforts continue to strengthen NIH's connection and commitment to the scientific community. NIH and individual IC activities are designed to improve communication and increase understanding of the revised NIH inclusion policy and 1997 OMB requirements for reporting racial and ethnic population data. Several documents are available in hard copy and online to assist investigators to appropriately address women and minority inclusion issues throughout the research grant and contract process. These include the following.

- A PowerPoint slide show, entitled "Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!," is a useful tool for investigators, faculty, and others in the scientific community and illustrates how research teams must comply with the NIH Inclusion policy in order to receive funding. It provides updated information on the revised policy and helpful guidance for submitting an NIH application, as well as where to find additional information on the current standards for compliance with NIH human subjects research.

- The *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*, revised in 2003, is a publication for the research community and NIH staff. This publication discusses the elements of recruitment and retention, the NIH inclusion policy, and 1997 OMB requirements for reporting race and ethnicity data, application submission, peer review, and funding. The publication is available on the ORWH website *http://orwh.od.nih.gov* and the NIH website for the inclusion of women and minorities policy implementation at: *http://grants1.nih.gov/grants/funding/women_min/women_min.htm*.

- The *Frequently Asked Questions (FAQs) for the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research* complements the *Outreach Notebook* and provides additional guidance to researchers and NIH staff in a user friendly format. The FAQs is available on the ORWH website *http://orwh.od.nih.gov/* and the NIH website for the inclusion of women and minorities policy implementation at: *http://grants1.nih.gov/grants/funding/women_min/women_min.htm*.

While NIH staff have been trained on the updated guidelines for monitoring inclusion of women and minorities in clinical research and how to effectively provide outreach to the research community, investigators are instructed to address women and minority inclusion issues in the development of their applications and proposals for clinical research.

Monitoring Compliance: Extramural and Intramural Population Data Analysis

When assessing inclusion data, enrollment figures should not be directly compared to the national census figures. The goal of the NIH policy is not to satisfy any quotas for proportional representation, but rather to conduct biomedical and behavioral research in such a manner that the scientific knowledge acquired will be generalizable to the entire population of the United States. The numbers of women or minority subgroups included in a particular study depends upon the scientific question addressed in

the study and the prevalence among women and minority subpopulations of the disease, disorder, or condition under investigation. Initial Review Groups are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study.

NIH has monitored aggregate demographic data for study populations through the existing NIH computerized tracking system since FY 1994 and tracking the inclusion of women and minorities in clinical studies has been implemented in all ICs. The NIH Tracking and Inclusion Committee continues to work on ways to refine and improve data collection methods and the quality of the data entered by each IC into this system. In May 2002, NIH successfully deployed a new population tracking system for monitoring the inclusion of women and minorities in clinical research. This system provides easier data entry and project monitoring for NIH staff, creates clear and timely NIH reports on inclusion data, incorporates the 1997 OMB standards for the classification of federal data on race and ethnicity, and is consistent with the newly revised PHS Form 398 and PHS Form 2590 (revised May, 2001). Following the implementation of the population tracking module, an eRA Population Tracking User Group consisting of representatives from several ICs, was formed to evaluate the system, recommend improvements and modifications, and provide continuous feedback related to system use. The re-engineered population tracking system continues to be refined based on input from the NIH user community.

- NIH has published an online users guide and began offering 2-hour population tracking system demonstrations, as well as in-depth, hands-on training sessions on the use of the population tracking system.

The aggregate data enable NIH to measure inclusion in order to formulate more specific questions about gaps in enrollment and to design studies to respond to those questions. Data compiled in future years will allow for longitudinal examination of trends and continued monitoring of compliance.

A review of intramural inclusion data indicates that the intramural research program is compliant with the reporting requirements adhered to by the extramural community and outlined in the *NIH Implementation Guidelines on the Inclusion of Women and Minority Subjects in Research Studies*. The Clinical Center Medical Executive Committee (MEC) has taken a leading role in assuring that investigators conducting clinical research protocols in the Clinical Center are trained and competent in the conduct of clinical research. To this end, the MEC designed and endorsed the Standards for Clinical Research within the NIH Intramural Research Program. This set of standards, endorsed by the Clinical Center's Board of Governors and the NIH institute directors, sets forth guidelines for the infrastructure, training, education, and monitoring required for safe and effective conduct of clinical research. The Clinical Center is also actively engaged in outreach to minority groups to encourage participation in intramural clinical research.

Format Changes for Reporting Race and Ethnicity Data Beginning in FY 2002

The 1997 OMB Directive 15 minimum standards for maintaining, collecting, and reporting data on race and ethnicity directs changes in how data are reported to NIH. The FY 2003 and FY 2004 tables describe data using both the 1977 and 1997 OMB standards for reporting data on race and ethnicity. Implementation of the 1997 OMB standards involved a number of changes, including collecting and reporting information on race and ethnicity separately (Hispanic/Latinos are considered an ethnicity and reported separately from racial data); using the new definitions and categories for ethnicity and race (a separate racial category for Asian population data and Hawaiian/Pacific Islander data); and allowing respondents the option of selection more than one race or only one race.

The 1997 OMB reporting format does not allow aggregation of ethnic and racial data with similar data collected under the 1977 OMB standards because the categories and methods for collecting the data are

fundamentally different. Changes in the standardization of definitions and business rules across NIH for improving the data entered in the population tracking system are reflected in data reported beginning in FY 2002. This transition period makes comparisons with prior FY 2002 data difficult. However, implementation of these changes will improve the consistency and comparability for future reporting.

Summary Report of NIH Inclusion Data

NIH Aggregate Extramural and Intramural Population Data Reported in FY 2003 and FY 2004

Tables 7 to 27 provide aggregate enrollment data for extramural and intramural research protocols funded in FY 2003 and FY 2004. Previous inclusion reports and aggregate enrollment figures for women, men, and minority groups for FY 1994 to the present can be found on the ORWH website at *http://orwh.od.nih.gov/inclusion.html*. For this biennial report, the FY 2003 and FY 2004 data tables have been reformatted and some tables may vary slightly from prior reported summary data. Some additional data has been presented.

Analysis of the FY 2003 and FY 2004 inclusion data show that substantial numbers of women, non-minority men, and minorities have been included as research subjects in Phase III clinical trials and other human subject research studies, in both intramural and extramural programs.

Extramural Research: FY 2003 and FY 2004

In FY 2003, more than 12 million participants were reported for all extramural clinical research, including Phase III clinical trials and other clinical studies. A snapshot of the aggregate enrollment data shows that approximately 60 percent were women, 39.9 percent were men, and 0.9 percent did not identify a sex/gender. (Table 11) Correspondingly, in FY 2004, more than 16 million participants were reported for all extramural clinical research, including Phase III clinical trials and other clinical studies, an increase of about 4 million participants. Of the 16 million participants, approximately 58.6 percent were women, 39.8 percent were men, and 1.6 percent did not provide sex identification. (Table 13) While the number of participants in clinical research significantly increased, there was no substantial percentage change in the ratio of women and men. However, when sex-specific studies were excluded, the proportions of women and men in all clinical research were proportional to the percentages of the general population. (See Tables 12 and 14)

Aggregate enrollment data reported in FY 2003 for extramural Phase III trials show that approximately 55.4 percent of the participants were women. Of the 635 extramural Phase III research protocols that continue to report following the 1977 OMB standards, minority representation was highest for blacks (not Hispanic) at 11.6 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics comprised approximately 6.7 percent, Asian/Pacific Islanders 1.83 percent and whites (not Hispanic) 77.2 percent of the participants. The categories Hawaiian/Pacific Islander and More Than One Race were not designations with the 1977 OMB standards and, therefore, no data were reported in these categories. (Table 15)

In FY 2003, there were 196 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Accordingly, minority representation by race was highest for blacks at 28.3 percent and lowest for Hawaiian/Pacific Islanders at 0.2 percent. Asians represented 2.71 percent, American Indian/Alaska Natives 0.53 percent and whites 57.1 percent. Approximately 1.04 percent of the participants identified More Than One Race for their racial category. Of the 196 extramural Phase III research protocols designating an ethnicity in FY 2003, 77.5 percent identified a racial category and an ethnicity of not Hispanic. Whereas, 9.71 percent identified a racial category and an ethnic category of Hispanic/Latino, 13.7 percent of participants identified a racial category, but did not report an ethnicity. (Table 15)

Aggregate enrollment data for extramural Phase III trials reported in FY 2004 show that approximately 55.9 percent were women. Of the 273 extramural Phase III research

Table 7. Overview of NIH Extramural and Intramural Clinical Research: Number of Protocols and Enrollment by Sex, Reported In FY 2003

Protocols Reported	Clinical Studies (Not NIH Defined Phase III)	NIH Defined Phase III Clinical Trials*	Total All Clinical Studies
Protocols with Enrollment	9,352	864	**10,216**
%	71.6%	88.4%	72.8%
Protocols with zero enrollment. Enrollment data has not yet been submitted	3,712	113	3,825
	28.4%	11.6%	27.2%
Total Number of Protocols	**13,064**	**977**	**14,041**
%	100.0%	100.0%	**100.0%**

Enrollment Reported	Clinical Studies (Not NIH Defined Phase III)	NIH Defined Phase III Clinical Trials	Total All Clinical Studies
Females Enrolled	8,220,593	293,888	8,514,481
%	57.7%	55.1%	57.6%
Males Enrolled	5,883,897	237,599	6,121,496
%	41.3%	44.5%	41.4%
Sex of Subjects is Unknown	134,285	1,992	136,277
%	0.9%	0.4%	0.9%
Total Subjects Enrolled	**14,238,775**	**533,479**	**14,772,254**
%	100.0%	100.0%	100.0%

* An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Table 8. Overview of NIH Extramural and Intramural Clinical Research: Number of Protocols and Enrollment by Sex, Reported In FY 2004

Protocols Reported	Clinical Studies (Not NIH Defined Phase III)	NIH Defined Phase III Clinical Trials*	Total All Clinical Studies
Protocols with Enrollment	9,549	576	**10,125**
%	69.1%	83.2%	69.8%
Protocols with zero enrollment. Enrollment data has not yet been submitted	4,271	116	4,387
	30.9%	16.8%	30.2%
Total Number of Protocols	**13,820**	**692**	**14,512**
%	100.0%	100.0%	**100.0%**

Enrollment Reported	Clinical Studies (Not NIH Defined Phase III)	NIH Defined Phase III Clinical Trials	Total All Clinical Studies
Females Enrolled	10,602,296	286,801	10,889,097
%	57.6%	55.5%	57.5%
Males Enrolled	7,513,411	228,481	7,741,892
%	40.8%	44.2%	40.9%
Sex of Subjects is Unknown	291,853	1,078	292,931
%	1.6%	0.2%	1.5%
Total Subjects Enrolled	**18,407,560**	**516,360**	**18,923,920**
%	100.0%	100.0%	100.0%

* An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.

Table 9. Summary of NIH Extramural and Intramural Clinical Research Enrollment by Race and Ethnicity, Reported in FY 2003 and FY 2004

These data are obtained from the NIH population tracking data system for clinical research studies. Investigators report enrollment data using either the "Old Form" or the "New Form". New studies are using only the "New Form"; therefore, the totals on the "Old Form" are declining over time while the totals on the "New Form" are increasing.

NOTE 1: The data from the Old Form (1977 OMB Standards, combined race/ethnicity format) and the New Form (1997 OMB Standards, separate race and ethnicity formats) cannot be accurately combined for a specific category; e.g., in 1997, "Asian" is a separate race than "Hawaiian/Pacific Islander"; and "Hispanic or Latino" in the New form is reported also by racial category and included in the appropriate columns under "Total of All Subjects by Race".

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format									
FY Funded	FY Reported	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total	Minority Total
2002	2003	36,579	730,542	472,426	288,523	3,238,284	278,901	5,045,255	**1,528,070**
	%	0.73%	14.48%	9.36%	5.72%	64.18%	5.53%	100.00%	**30.29%**
2003	2004	29,387	307,052	342,188	214,322	2,348,529	172,130	3,413,608	**892,949**
	%	0.86%	8.99%	10.02%	6.28%	68.80%	5.04%	100.00%	**26.16%**

New Form: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats														
		Total of All Subjects by Race									Total of All Subjects by Ethnicity			
FY Funded	FY Reported	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Minority Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
2002	2003	63,544	2,138,002	960,090	37,569	5,415,710	99,462	1,012,622	*9,726,999*	**3,199,205**	8,162,259	611,641	953,099	*9,726,999*
	%	0.65%	21.98%	9.87%	0.39%	55.68%	1.02%	10.41%	*100.00%*	**32.89%**	83.91%	6.29%	9.80%	*100.00%*
2003	2004	98,047	4,345,396	1,379,857	54,452	8,065,069	186,241	1,381,250	*15,510,312*	**5,877,752**	13,168,842	756,339	1,585,131	*15,510,312*
	%	0.63%	28.02%	8.90%	0.35%	52.00%	1.20%	8.91%	*100.00%*	**37.90%**	84.90%	4.88%	10.22%	*100.00%*

NOTE 2: Summary Totals are provided for two years for the Old Form and the New Form. The Summary Minority Total Estimate (the sum of Old and New Forms) is only an estimate of the total Minority enrollment.

Summary Totals: Old + New Forms					
FY Funded	FY Reported		Total		Summary Minority Total Estimate
2002	2003		14,772,254		**4,727,275**
	%		100%		**32.00%**
2003	2004		18,923,920		**6,770,701**
	%		100%		**35.78%**

Table 10. Summary of NIH Extramural and Intramural Phase III Clinical Research Enrollment by Race and Ethnicity, Reported in FY 2003 and FY 2004

NOTE: Table 5 includes ONLY NIH Defined Phase III Clinical Trials, which are a subset of all clinical trials. In May 2005, applicants using the PHS 398 will be required to identify when their proposed study is a clinical trial.

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format									
FY Funded	FY Reported	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown/ Other	Total	Minority Total
2002	2003	1,703	20,050	50,186	29,402	338,269	16,666	456,276	**101,341**
	%	0.37%	4.39%	11.00%	6.44%	74.14%	3.65%	100.00%	**22.21%**
2003	2004	1,439	18,574	43,953	32,085	257,894	13,864	367,809	**96,051**
	%	0.39%	5.05%	11.95%	8.72%	70.12%	3.77%	100.00%	**26.11%**

New Form: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats														
		Total of All Subjects by Race									Total of All Subjects by Ethnicity			
FY Funded	FY Reported	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown /Other	Total	Minority Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
2002	2003	407	2,096	21,892	116	44,086	804	7,802	*77,203*	**24,511**	59,882	7,486	9,835	*77,203*
	%	0.53%	2.71%	28.36%	0.15%	57.10%	1.04%	10.11%	*100.00%*	**31.75%**	77.56%	9.70%	12.74%	*100.00%*
2003	2004	1,219	3,647	36,136	442	98,703	3,839	4,565	*148,551*	**41,444**	128,370	12,650	7,531	*148,551*
	%	0.82%	2.46%	24.33%	0.30%	66.44%	2.58%	3.07%	*100.00%*	**27.90%**	86.41%	8.52%	5.07%	*100.00%*

NOTE 2: Summary Totals are provided for two years for the Old Form and the New Form. The Summary Minority Total Estimate (the sum of Old and New Forms) is only an estimate of the total minority enrollment.

SUMMARY TOTALS: Old Form + New Form				
FY Funded	FY Reported	Total, Old + New Form		Summary Minority Total Estimate- Old Form + New Form
2002	2003	533,479		125,852
	%	100%		24%
2003	2004	516,360		137,495
	%	100%		27%

Table 11. Aggregate Enrollment Data for All Extramural Research Protocols Reported in FY 2003: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	8,964	287,709	230,397	142,009	1,159,679	81,692	1,910,450
	0.28%	**8.95%**	**7.17%**	**4.42%**	**36.08%**	**2.54%**	**59.44%**
	0.47%	*15.06%*	*12.06%*	*7.43%*	*60.70%*	*4.28%*	*100.00%*
	49.33%	***53.44%***	***62.43%***	***61.70%***	***60.77%***	***54.38%***	***59.44%***
Male	7,149	243,553	136,148	86,874	741,621	56,695	1,272,040
	0.22%	**7.58%**	**4.24%**	**2.70%**	**23.07%**	**1.76%**	**39.57%**
	0.56%	*19.15%*	*10.70%*	*6.83%*	*58.30%*	*4.46%*	*100.00%*
	39.34%	***45.24%***	***36.89%***	***37.74%***	***38.86%***	***37.74%***	***39.57%***
Unknown	2,059	7,080	2,510	1,294	7,017	11,838	31,798
	0.064%	**0.22%**	**0.08%**	**0.04%**	**0.22%**	**0.37%**	**0.99%**
	6.48%	*22.27%*	*7.89%*	*4.07%*	*22.07%*	*37.23%*	*100.00%*
	11.33%	***1.32%***	***0.68%***	***0.56%***	***0.37%***	***7.88%***	***0.99%***
Total	18,172	538,342	369,055	230,177	1,908,317	150,225	3,214,288
	0.57%	**16.75%**	**11.48%**	**7.16%**	**59.37%**	**4.67%**	**100.00%**
	0.57%	*16.75%*	*11.48%*	*7.16%*	*59.37%*	*4.67%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 3,704

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

More females (7,644,451 or 59.1%) than males (5,172,748 or 39.9%) are enrolled in aggregate extramural research protocols.

Largest identified racial group is White at 59.37% following the 1977 OMB standards and 55.67% following the 1997 OMB standards.

Largest identified racial minority group is Asian at 16.75% following the 1977 OMB standards and 21.9% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Native at (0.6%).

According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islander at (0.4%).

6.3% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 7.2% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 5,157

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	42,920	769,183	602,381	16,157	3,503,244	55,687	744,429	5,734,001	4,652,012	378,509	703,480	5,734,001
	0.44%	**7.91%**	**6.19%**	**0.17%**	**36.03%**	**0.57%**	**7.66%**	**58.97%**	**47.84%**	**3.89%**	**7.23%**	**58.97%**
	0.75%	*13.41%*	*10.51%*	*0.28%*	*61.10%*	*0.97%*	*12.98%*	*100.00%*	*81.13%*	*6.60%*	*12.27%*	*100.00%*
	67.56%	***35.98%***	***62.78%***	***43.01%***	***64.71%***	***55.99%***	***73.53%***	***58.97%***	***57.01%***	***61.90%***	***73.81%***	***58.97%***
Male	19,229	1,366,927	349,343	15,638	1,895,347	43,321	210,903	3,900,708	3,486,972	230,768	182,968	3,900,708
	0.20%	**14.06%**	**3.59%**	**0.16%**	**19.49%**	**0.45%**	**2.17%**	**40.11%**	**35.86%**	**2.37%**	**1.88%**	**40.11%**
	0.49%	*35.04%*	*8.96%*	*0.40%*	*48.59%*	*1.11%*	5.41%	*100.00%*	*89.39%*	*5.92%*	*4.69%*	*100.00%*
	30.27%	***63.94%***	***36.41%***	***41.63%***	***35.01%***	***43.56%***	***20.83%***	***40.11%***	***42.74%***	***37.74%***	***19.20%***	***40.11%***
Unknown	1,383	1,712	7,829	5,773	14,934	448	57,114	89,193	20,400	2,201	66,592	89,193
	0.01%	**0.02%**	**0.08%**	**0.06%**	**0.15%**	**0.00%**	***0.59%***	**0.92%**	**0.21%**	**0.02%**	**0.68%**	**0.92%**
	1.55%	*1.92%*	*8.78%*	6.47%	*16.74%*	*0.50%*	*64.03%*	*100.00%*	*22.87%*	*2.47%*	*74.66%*	*100.00%*
	2.18%	***0.08%***	***0.82%***	***15.37%***	***0.28%***	***0.45%***	***5.64%***	***0.92%***	***0.25%***	***0.36%***	***6.99%***	***0.92%***
Total	63,532	2,137,822	959,553	37,568	5,413,525	99,456	1,012,446	9,723,902	8,159,384	611,478	953,040	9,723,902
	0.65%	**21.99%**	**9.87%**	**0.39%**	**55.67%**	**1.02%**	**10.41%**	**100.00%**	**83.91%**	**6.29%**	**9.80%**	**100.00%**
	0.65%	*21.99%*	*9.87%*	*0.39%*	*55.67%*	*1.02%*	*10.41%*	*100.00%*	*83.91%*	*6.29%*	*9.80%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL Females	7,644,451	TOTAL Males	5,172,748	TOTAL Unknown	120,991	OVERALL Total	12,938,190
	59.08%		39.98%		0.94%		100%

Total Number of Protocols with Enrollment Data: 8,861

Table 12: Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Reported in FY2003

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	7,541	251,238	153,109	91,828	650,776	70,595	1,225,087
	0.32%	**10.64%**	**6.48%**	**3.89%**	**27.55%**	**2.99%**	**51.87%**
	0.62%	*20.51%*	*12.50%*	*7.50%*	*53.12%*	*5.76%*	*100.00%*
	45.67%	***50.63%***	***54.62%***	***52.10%***	***51.06%***	***59.82%***	***51.87%***
Male	6,911	237,929	124,693	83,146	616,728	35,579	1,104,986
	0.29%	**10.07%**	**5.28%**	**3.52%**	**26.11%**	**1.51%**	**46.78%**
	0.63%	*21.53%*	*11.28%*	*7.52%*	*55.81%*	*3.22%*	*100.00%*
	41.86%	***47.95%***	***44.48%***	***47.17%***	***48.39%***	***30.15%***	***46.78%***
Unknown	2,059	7,080	2,510	1,294	7,017	11,838	31,798
	0.087%	**0.30%**	**0.11%**	**0.05%**	**0.30%**	**0.50%**	**1.35%**
	6.48%	*22.27%*	*7.89%*	*4.07%*	*22.07%*	*37.23%*	*100.00%*
	12.47%	***1.43%***	***0.90%***	***0.73%***	***0.55%***	***10.03%***	***1.35%***
Total	16,511	496,247	280,312	176,268	1,274,521	118,012	2,361,871
	0.70%	**21.01%**	**11.87%**	**7.46%**	**53.96%**	**5.00%**	**100.00%**
	0.70%	*21.01%*	*11.87%*	*7.46%*	*53.96%*	*5.00%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 2,901

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 8,861 protocols of which 1,280 were *female-only* protocols and 519 were *male-only* protocols.
Excluding sex-specific studies, the number of females (4,815,256 or 49.1%) to males (4,864,138 or 49.6%) enrolled in extramural research protocols are closely representative of the general population.
Largest identified racial group is White at 53.9% following the 1977 OMB standards and 53.4% following the 1997 OMB standards.
Largest identified racial minority group is Asian/Pacific Islanders at 21% following the 1977 OMB standards and 27.5% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.7%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.49%).
6.3% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards, whereas 7.5% of participants identified as Hispanic according to 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 4,161

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	19,882	712,983	401,586	14,828	2,146,846	45,306	248,738	3,590,169	3,126,733	243,467	219,969	3,590,169
	0.27%	**9.59%**	**5.40%**	**0.20%**	**28.86%**	**0.61%**	**3.34%**	**48.26%**	**42.03%**	**3.27%**	**2.96%**	**48.26%**
	0.55%	*19.86%*	*11.19%*	*0.41%*	*59.80%*	*1.26%*	*6.93%*	*100.00%*	*87.09%*	*6.78%*	*6.13%*	*100.00%*
	49.45%	***34.84%***	***53.88%***	***41.00%***	***54.00%***	***51.89%***	***49.02%***	***48.26%***	***48.05%***	***51.89%***	***47.66%***	***48.26%***
Male	18,938	1,331,988	335,965	15,569	1,813,589	41,563	201,540	3,759,152	3,360,703	223,511	174,938	3,759,152
	0.25%	**17.91%**	**4.52%**	**0.21%**	**24.38%**	**0.56%**	**2.71%**	**50.54%**	**45.18%**	**3.00%**	**2.35%**	**50.54%**
	0.50%	*35.43%*	*8.94%*	*0.41%*	*48.24%*	*1.11%*	5.36%	*100.00%*	*89.40%*	*5.95%*	*4.65%*	*100.00%*
	47.11%	***65.08%***	***45.07%***	***43.04%***	***45.62%***	***47.60%***	***39.72%***	***50.54%***	***51.64%***	***47.64%***	***37.91%***	***50.54%***
Unknown	1,383	1,712	7,829	5,773	14,934	448	57,114	89,193	20,400	2,201	66,592	89,193
	0.02%	**0.02%**	**0.11%**	**0.08%**	**0.20%**	**0.01%**	***0.77%***	**1.20%**	**0.27%**	**0.03%**	**0.90%**	**1.20%**
	1.55%	*1.92%*	*8.78%*	6.47%	*16.74%*	*0.50%*	*64.03%*	*100.00%*	*22.87%*	*2.47%*	*74.66%*	*100.00%*
	3.44%	***0.08%***	***1.05%***	***15.96%***	***0.38%***	***0.51%***	***11.26%***	***1.20%***	***0.31%***	***0.47%***	***14.43%***	***1.20%***
Total	40,203	2,046,683	745,380	36,170	3,975,369	87,317	507,392	7,438,514	6,507,836	469,179	461,499	7,438,514
	0.54%	**27.51%**	**10.02%**	**0.49%**	**53.44%**	**1.17%**	**6.82%**	**100.00%**	**87.49%**	**6.31%**	**6.20%**	**100.00%**
	0.54%	*27.51%*	*10.02%*	*0.49%*	*53.44%*	*1.17%*	*6.82%*	*100.00%*	*87.49%*	*6.31%*	*6.20%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form						
TOTAL		TOTAL		TOTAL		OVERALL
Females	4,815,256	Males	4,864,138	Unknown	120,991	Total 9,800,385
	49.13%		49.63%		1.23%	100%

Total Number of Protocols with Enrollment Data: 7,062

Table 13. Aggregate Enrollment Data for All Extramural Research Protocols Reported in FY 2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	6,366	68,746	151,718	85,891	615,764	22,920	951,405
	0.42%	**4.49%**	**9.91%**	**5.61%**	**40.23%**	**1.50%**	**62.16%**
	0.67%	*7.23%*	*15.95%*	*9.03%*	*64.72%*	*2.41%*	*100.00%*
	58.76%	***62.51%***	***64.13%***	***61.72%***	***62.08%***	***54.39%***	***62.16%***
Male	4,391	40,875	81,883	52,154	373,856	14,787	567,946
	0.29%	**2.67%**	**5.35%**	**3.41%**	**24.43%**	**0.97%**	**37.11%**
	0.77%	*7.20%*	*14.42%*	*9.18%*	*65.83%*	*2.60%*	*100.00%*
	40.53%	***37.17%***	***34.61%***	***37.48%***	***37.69%***	***35.09%***	***37.11%***
Unknown	76	353	2,979	1,119	2,305	4,434	11,266
	0.005%	**0.02%**	**0.19%**	**0.07%**	**0.15%**	**0.29%**	**0.74%**
	0.67%	*3.13%*	*26.44%*	*9.93%*	*20.46%*	*39.36%*	*100.00%*
	0.70%	***0.32%***	***1.26%***	***0.80%***	***0.23%***	***10.52%***	***0.74%***
Total	10,833	109,974	236,580	139,164	991,925	42,141	1,530,617
	0.71%	**7.18%**	**15.46%**	**9.09%**	**64.81%**	**2.75%**	**100.00%**
	0.71%	*7.18%*	*15.46%*	*9.09%*	*64.81%*	*2.75%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 1,831

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

More females (9,945,981 or 58.6%) than males (6,754,928 or 39.8%) are enrolled in aggregate extramural research protocols.
Largest identified racial group is Whites at 64.8% following the 1977 OMB standards and 52% following the 1997 OMB standards.
Largest identified racial minority group is Blacks at 15.46% following the 1977 OMB standards.
Largest identified racial minority group is Asians at 28.1% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.7%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.35%).
4.8% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards, whereas 9% of participants identified as Hispanic according to 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 6,903

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	66,063	1,915,721	840,059	28,339	5,044,861	103,608	995,925	8,994,576	7,390,050	472,368	1,132,158	8,994,576
	0.43%	**12.40%**	**5.44%**	**0.18%**	**32.66%**	**0.67%**	**6.45%**	**58.23%**	**47.84%**	**3.06%**	**7.33%**	**58.23%**
	0.73%	*21.30%*	*9.34%*	*0.32%*	*56.09%*	*1.15%*	*11.07%*	*100.00%*	*82.16%*	*5.25%*	*12.59%*	*100.00%*
	67.87%	***44.11%***	***61.14%***	***52.05%***	***62.95%***	***55.67%***	***72.33%***	***58.23%***	***56.38%***	***62.60%***	***71.47%***	***58.23%***
Male	29,706	2,415,164	517,220	23,839	2,820,402	81,024	299,627	6,186,982	5,535,928	275,989	375,065	6,186,982
	0.19%	**15.64%**	**3.35%**	**0.15%**	**18.26%**	**0.52%**	**1.94%**	**40.06%**	**35.84%**	**1.79%**	**2.43%**	**40.06%**
	0.48%	*39.04%*	*8.36%*	*0.39%*	*45.59%*	*1.31%*	4.84%	*100.00%*	*89.48%*	*4.46%*	*6.06%*	*100.00%*
	30.52%	***55.61%***	***37.64%***	***43.78%***	***35.19%***	***43.54%***	***21.76%***	***40.06%***	***42.24%***	***36.58%***	***23.68%***	***40.06%***
Unknown	1,564	11,843	16,711	2,270	149,289	1,479	81,397	264,553	181,424	6,168	76,961	264,553
	0.01%	**0.08%**	**0.11%**	**0.01%**	**0.97%**	**0.01%**	***0.53%***	**1.71%**	**1.17%**	**0.04%**	**0.50%**	**1.71%**
	0.59%	*4.48%*	6.32%	*0.86%*	*56.43%*	*0.56%*	*30.77%*	*100.00%*	*68.58%*	*2.33%*	*29.09%*	*100.00%*
	1.61%	***0.27%***	***1.22%***	***4.17%***	***1.86%***	***0.79%***	***5.91%***	***1.71%***	***1.38%***	***0.82%***	***4.86%***	***1.71%***
Total	97,333	4,342,728	1,373,990	54,448	8,014,552	186,111	1,376,949	15,446,111	13,107,402	754,525	1,584,184	15,446,111
	0.63%	**28.12%**	**8.90%**	**0.35%**	**51.89%**	**1.20%**	**8.91%**	**100.00%**	**84.86%**	**4.88%**	**10.26%**	**100.00%**
	0.63%	*28.12%*	*8.90%*	*0.35%*	*51.89%*	*1.20%*	*8.91%*	*100.00%*	*84.86%*	*4.88%*	*10.26%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	9,945,981	Males	6,754,928	Unknown	275,819	Total	16,976,728
	58.59%		39.79%		1.62%		100%

Total Number of Protocols with Enrollment Data: 8,734

Table 14: Aggregate Enrollment Data for Extramural Research Protocols Excluding Male-Only and Female-Only Protocols Reported in FY2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	5,107	45,875	94,686	57,592	325,993	17,185	546,438
	0.49%	**4.38%**	**9.04%**	**5.50%**	**31.13%**	**1.64%**	**52.17%**
	0.93%	*8.40%*	*17.33%*	*10.54%*	*59.66%*	*3.14%*	*100.00%*
	54.64%	***54.35%***	***56.56%***	***53.51%***	***50.70%***	***48.36%***	***52.17%***
Male	4,163	38,172	69,755	48,924	314,694	13,914	489,622
	0.40%	**3.64%**	**6.66%**	**4.67%**	**30.05%**	**1.33%**	**46.75%**
	0.85%	*7.80%*	*14.25%*	*9.99%*	*64.27%*	*2.84%*	*100.00%*
	44.54%	***45.23%***	***41.66%***	***45.45%***	***48.94%***	***39.16%***	***46.75%***
Unknown	76	353	2,979	1,119	2,305	4,434	11,266
	0.007%	**0.03%**	**0.28%**	**0.11%**	**0.22%**	**0.42%**	**1.08%**
	0.67%	*3.13%*	*26.44%*	*9.93%*	*20.46%*	*39.36%*	*100.00%*
	0.81%	***0.42%***	***1.78%***	***1.04%***	***0.36%***	***12.48%***	***1.08%***
Total	9,346	84,400	167,420	107,635	642,992	35,533	1,047,326
	0.89%	**8.06%**	**15.99%**	**10.28%**	**61.39%**	**3.39%**	**100.00%**
	0.89%	*8.06%*	*15.99%*	*10.28%*	*61.39%*	*3.39%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 1,490

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 8,734 protocols of which 1,336 were *female-only* protocols and 86 were *male-only* protocols. Excluding sex-specific studies, the number of females (6,948,656 or 50.4%) to males (6,560,527 or 47.6%) enrolled in intramural research protocols are closely representative of the general population.
Largest identified racial group is White at 61.4% following the 1977 OMB standards and 50.3% following the 1997 OMB standards.
Largest identified racial minority group is Blacks at 16% following the 1977 OMB standards.
Largest identified racial minority group is Asians at 32.5% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.9%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.41%).

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 5,482

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	32,092	1,755,601	659,165	25,711	3,478,447	88,580	362,622	6,402,218	5,632,779	288,516	480,923	6,402,218
	0.25%	**13.78%**	**5.18%**	**0.20%**	**27.31%**	**0.70%**	**2.85%**	**50.26%**	**44.22%**	**2.27%**	**3.78%**	**50.26%**
	0.50%	*27.42%*	*10.30%*	*0.40%*	*54.33%*	*1.38%*	*5.66%*	*100.00%*	*87.98%*	*4.51%*	*7.51%*	*100.00%*
	50.83%	***42.46%***	***56.01%***	***49.81%***	***54.34%***	***52.21%***	***48.99%***	***50.26%***	***50.10%***	***51.04%***	***51.78%***	***50.26%***
Male	29,476	2,366,994	500,980	23,636	2,773,778	79,603	296,238	6,070,705	5,429,380	270,603	370,922	6,070,905
	0.23%	**18.58%**	**3.93%**	**0.19%**	**21.78%**	**0.62%**	**2.33%**	**47.66%**	**42.62%**	**2.12%**	**2.91%**	**47.66%**
	0.49%	*38.99%*	*8.25%*	*0.39%*	*45.69%*	*1.31%*	4.88%	*100.00%*	*89.43%*	*4.46%*	*6.11%*	*100.00%*
	46.69%	***57.25%***	***42.57%***	***45.79%***	***43.33%***	***46.92%***	***40.02%***	***47.66%***	***48.29%***	***47.87%***	***39.94%***	***47.66%***
Unknown	1,564	11,843	16,711	2,270	149,289	1,479	81,397	264,553	181,424	6,168	76,961	264,553
	0.01%	**0.09%**	**0.13%**	**0.02%**	**1.17%**	**0.01%**	***0.64%***	**2.08%**	**1.42%**	**0.05%**	**0.60%**	**2.08%**
	0.59%	*4.48%*	6.32%	*0.86%*	*56.43%*	*0.56%*	*30.77%*	*100.00%*	*68.58%*	*2.33%*	*29.09%*	*100.00%*
	2.48%	***0.29%***	***1.42%***	***4.40%***	***2.33%***	***0.87%***	***11.00%***	***2.08%***	***1.61%***	***1.09%***	***8.29%***	***2.08%***
Total	63,132	4,134,438	1,176,856	51,617	6,401,514	169,662	740,257	12,737,476	11,243,583	565,287	928,806	12,737,676
	0.50%	**32.46%**	**9.24%**	**0.41%**	**50.26%**	**1.33%**	**5.81%**	**100.00%**	**88.27%**	**4.44%**	**7.29%**	**100.00%**
	0.50%	*32.46%*	*9.24%*	*0.41%*	*50.26%*	*1.33%*	*5.81%*	*100.00%*	*88.27%*	*4.44%*	*7.29%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL Females	6,948,656	TOTAL Males	6,560,527	TOTAL Unknown	275,819	OVERALL Total	13,785,002
	50.41%		47.59%		2.00%		100%

Total Number of Protocols with Enrollment Data: 6,972

Table 15. Aggregate Enrollment Data for Extramural Phase III Research Protocols Reported in FY 2003: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	1,038	4,744	29,109	16,302	190,387	4,565	246,145
	0.24%	**1.10%**	**6.76%**	**3.79%**	**44.22%**	**1.06%**	**57.18%**
	0.42%	*1.93%*	*11.83%*	*6.62%*	*77.35%*	*1.85%*	*100.00%*
	61.42%	***60.08%***	***58.53%***	***55.92%***	***57.31%***	***46.39%***	***57.18%***
Male	652	3,152	20,621	12,767	141,793	4,358	183,343
	0.15%	**0.73%**	**4.79%**	**2.97%**	**32.94%**	**1.01%**	**42.59%**
	0.36%	*1.72%*	*11.25%*	*6.96%*	*77.34%*	*2.38%*	*100.00%*
	38.58%	***39.92%***	***41.47%***	***43.79%***	***42.68%***	***44.28%***	***42.59%***
Unknown	0	0	1	84	20	918	1,023
	0.000%	**0.00%**	**0.00%**	**0.02%**	**0.00%**	**0.21%**	**0.24%**
	0.00%	*0.00%*	*0.10%*	*8.21%*	*1.96%*	*89.74%*	*100.00%*
	0.00%	***0.00%***	***0.00%***	***0.29%***	***0.01%***	***9.33%***	***0.24%***
Total	1,690	7,896	49,731	29,153	332,200	9,841	430,511
	0.39%	**1.83%**	**11.55%**	**6.77%**	**77.16%**	**2.29%**	**100.00%**
	0.39%	*1.83%*	*11.55%*	*6.77%*	*77.16%*	*2.29%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 635

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

Substantial numbers of women and minorities are enrolled in Phase III research protocols reported in FY2003.

More females (281,299 or 55.4%) than males (224,169 or 44.2%) are enrolled in aggregate extramural research protocols.

Largest identified racial group is Whites at 77.2% following the 1977 OMB standards and 57.1% following the 1997 OMB standards.

Largest identified racial minority group is Blacks at 11.6% following the 1977 OMB standards and 28.3% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.4%).

According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.20%).

10% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 6.7% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 196

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	164	964	12,546	47	18,355	454	2,624	35,154	26,928	2,739	5,487	35,154
	0.21%	**1.25%**	**16.30%**	**0.06%**	**23.85%**	**0.59%**	**3.41%**	**45.69%**	**35.00%**	**3.56%**	**7.13%**	**45.69%**
	0.47%	*2.74%*	*35.69%*	*0.13%*	*52.21%*	*1.29%*	*7.46%*	*100.00%*	*76.60%*	*7.79%*	*15.61%*	*100.00%*
	40.29%	***46.15%***	***57.54%***	***40.87%***	***41.77%***	***56.54%***	***33.70%***	***45.69%***	***45.15%***	***36.65%***	***55.82%***	***45.69%***
Male	243	1,123	9,247	68	25,545	348	4,252	40,826	32,662	4,731	3,433	40,826
	0.32%	**1.46%**	**12.02%**	**0.09%**	**33.20%**	**0.45%**	**5.53%**	**53.06%**	**42.45%**	**6.15%**	**4.46%**	**53.06%**
	0.60%	*2.75%*	*22.65%*	*0.17%*	*62.57%*	*0.85%*	10.41%	*100.00%*	*80.00%*	*11.59%*	*8.41%*	*100.00%*
	59.71%	***53.76%***	***42.41%***	***59.13%***	***58.13%***	***43.34%***	***54.61%***	***53.06%***	***54.76%***	***63.30%***	***34.92%***	***53.06%***
Unknown	0	2	10	0	45	1	910	968	54	4	910	968
	0.00%	**0.00%**	**0.01%**	**0.00%**	**0.06%**	**0.00%**	***1.18%***	**1.26%**	**0.07%**	**0.01%**	**1.18%**	**1.26%**
	0.00%	*0.21%*	*1.03%*	0.00%	*4.65%*	*0.10%*	*94.01%*	*100.00%*	*5.58%*	*0.41%*	*94.01%*	*100.00%*
	0.00%	***0.10%***	***0.05%***	***0.00%***	***0.10%***	***0.12%***	***11.69%***	***1.26%***	***0.09%***	***0.05%***	***9.26%***	***1.26%***
Total	407	2,089	21,803	115	43,945	803	7,786	76,948	59,644	7,474	9,830	76,948
	0.53%	**2.71%**	**28.33%**	**0.15%**	**57.11%**	**1.04%**	**10.12%**	**100.00%**	**77.51%**	**9.71%**	**12.77%**	**100.00%**
	0.53%	*2.71%*	*28.33%*	*0.15%*	*57.11%*	*1.04%*	*10.12%*	*100.00%*	*77.51%*	*9.71%*	*12.77%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	281,299	Males	224,169	Unknown	1,991	Total	507,459
	55.43%		44.17%		0.39%		100%

Total Number of Protocols with Enrollment Data: 831

Table 16: Aggregate Enrollment Data for Extramural Phase III Protocols, Excluding Male-Only and Female-Only Protocols Reported in FY2003: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	476	1,487	15,509	10,778	60,941	2,129	91,320
	0.23%	**0.71%**	**7.40%**	**5.14%**	**29.09%**	**1.02%**	**43.59%**
	0.52%	*1.63%*	*16.98%*	*11.80%*	*66.73%*	*2.33%*	*100.00%*
	49.28%	***43.97%***	***50.36%***	***50.31%***	***41.46%***	***35.75%***	***43.59%***
Male	490	1,895	15,285	10,561	86,028	2,909	117,168
	0.23%	**0.90%**	**7.30%**	**5.04%**	**41.06%**	**1.39%**	**55.92%**
	0.42%	*1.62%*	*13.05%*	*9.01%*	*73.42%*	*2.48%*	*100.00%*
	50.72%	***56.03%***	***49.63%***	***49.30%***	***58.53%***	***48.84%***	***55.92%***
Unknown	0	0	1	84	20	918	1,023
	0.000%	**0.00%**	**0.00%**	**0.04%**	**0.01%**	**0.44%**	**0.49%**
	0.00%	*0.00%*	*0.10%*	*8.21%*	*1.96%*	*89.74%*	*100.00%*
	0.00%	***0.00%***	***0.00%***	***0.39%***	***0.01%***	***15.41%***	***0.49%***
Total	966	3,382	30,795	21,423	146,989	5,956	209,511
	0.46%	**1.61%**	**14.70%**	**10.23%**	**70.16%**	**2.84%**	**100.00%**
	0.46%	*1.61%*	*14.70%*	*10.23%*	*70.16%*	*2.84%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 413

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 831 protocols of which 189 were *female-only* protocols and 81 were *male-only* protocols. Excluding sex-specific studies, the number of females (118,082 or 43.4%) to males (152,217 or 55.9%) enrolled in extramural research protocols are closely representative of the general population.

Largest identified racial group is Whites at 70% following the 1977 OMB standards and 57.4% following the 1997 OMB standards.

Largest identified racial minority group is Blacks at 14.7% following the 1977 OMB standards and 27.6% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives (0.5%).

According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.2%).

9.7% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 10.2% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 148

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	93	840	8,679	40	14,645	207	2,258	26,762	19,192	2,192	5,378	26,762
	0.15%	**1.34%**	**13.82%**	**0.06%**	**23.33%**	**0.33%**	**3.60%**	**42.63%**	**30.57%**	**3.49%**	**8.57%**	**42.63%**
	0.35%	*3.14%*	*32.43%*	*0.15%*	*54.72%*	*0.77%*	*8.44%*	*100.00%*	*71.71%*	*8.19%*	*20.10%*	*100.00%*
	32.29%	***46.93%***	***50.13%***	***37.04%***	***40.65%***	***49.64%***	***33.03%***	***42.63%***	***40.88%***	***35.78%***	***55.40%***	***42.63%***
Male	195	948	8,623	68	21,337	209	3,669	35,049	27,699	3,931	3,419	35,049
	0.31%	**1.51%**	**13.74%**	**0.11%**	**33.99%**	**0.33%**	**5.84%**	**55.83%**	**44.12%**	**6.26%**	**5.45%**	**55.83%**
	0.56%	*2.70%*	*24.60%*	*0.19%*	*60.88%*	*0.60%*	10.47%	*100.00%*	*79.03%*	*11.22%*	*9.75%*	*100.00%*
	67.71%	***52.96%***	***49.81%***	***62.96%***	***59.23%***	***50.12%***	***53.66%***	***55.83%***	***59.00%***	***64.16%***	***35.22%***	***55.83%***
Unknown	0	2	10	0	45	1	910	968	54	4	910	968
	0.00%	**0.00%**	**0.02%**	**0.00%**	**0.07%**	**0.00%**	***1.45%***	**1.54%**	**0.09%**	**0.01%**	**1.45%**	**1.54%**
	0.00%	*0.21%*	*1.03%*	0.00%	*4.65%*	*0.10%*	*94.01%*	*100.00%*	*5.58%*	*0.41%*	*94.01%*	*100.00%*
	0.00%	***0.11%***	***0.06%***	***0.00%***	***0.12%***	***0.24%***	***13.31%***	***1.54%***	***0.12%***	***0.07%***	***9.37%***	***1.54%***
Total	288	1,790	17,312	108	36,027	417	6,837	62,779	46,945	6,127	9,707	62,779
	0.46%	**2.85%**	**27.58%**	**0.17%**	**57.39%**	**0.66%**	**10.89%**	**100.00%**	**74.78%**	**9.76%**	**15.46%**	**100.00%**
	0.46%	*2.85%*	*27.58%*	*0.17%*	*57.39%*	*0.66%*	*10.89%*	*100.00%*	*74.78%*	*9.76%*	*15.46%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form							
TOTAL		TOTAL		TOTAL		OVERALL	
Females	118,082	Males	152,217	Unknown	1,991	Total	272,290
	43.37%		55.90%		0.73%		100%

Total Number of Protocols with Enrollment Data: 561

Table 17. Aggregate Enrollment Data for Extramural Phase III Research Protocols Reported in FY 2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/	Asian/ Pacific	Black or African	Hispanic	White	Unknown/ Other	Total
Female	860	4,286	25,434	13,345	158,846	3,231	206,002
	0.26%	**1.28%**	**7.61%**	**3.99%**	**47.50%**	**0.97%**	**61.60%**
	0.42%	*2.08%*	*12.35%*	*6.48%*	*77.11%*	*1.57%*	*100.00%*
	60.78%	***67.90%***	***58.83%***	***57.14%***	***62.52%***	***53.48%***	***61.60%***
Male	554	2,026	17,800	9,928	95,224	2,729	128,261
	0.17%	**0.61%**	**5.32%**	**2.97%**	**28.47%**	**0.82%**	**38.35%**
	0.43%	*1.58%*	*13.88%*	*7.74%*	*74.24%*	*2.13%*	*100.00%*
	39.15%	***32.10%***	***41.17%***	***42.51%***	***37.48%***	***45.17%***	***38.35%***
Unknown	1	0	1	83	5	82	172
	0.000%	**0.00%**	**0.00%**	**0.02%**	**0.00%**	**0.02%**	**0.05%**
	0.58%	*0.00%*	*0.58%*	*48.26%*	*2.91%*	*47.67%*	*100.00%*
	0.07%	***0.00%***	***0.00%***	***0.36%***	***0.00%***	***1.36%***	***0.05%***
Total	1,415	6,312	43,235	23,356	254,075	6,042	334,435
	0.42%	**1.89%**	**12.93%**	**6.98%**	**75.97%**	**1.81%**	**100.00%**
	0.42%	*1.89%*	*12.93%*	*6.98%*	*75.97%*	*1.81%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 273

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

Substantial numbers of women and minorities are enrolled in Phase III research protocols reported in FY2004.
More females (269,715 or 55.9%) than males (211,532 or 43.8%) are enrolled in aggregate extramural research protocols.
Largest identified racial group is Whites at 77.9% following the 1977 OMB standards and 66.5% following the 1997 OMB standards.
Largest identified racial minority group is Blacks at 12.9% following the 1977 OMB standards and 24.3% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.4%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.30%).
8.5% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 7% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 266

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	802	1,657	18,865	114	38,304	2,078	1,893	63,713	55,738	5,051	2,924	63,713
	0.54%	**1.12%**	**12.76%**	**0.08%**	**25.90%**	**1.41%**	**1.28%**	**43.08%**	**37.69%**	**3.42%**	**1.98%**	**43.08%**
	1.26%	*2.60%*	*29.61%*	*0.18%*	*60.12%*	*3.26%*	*2.97%*	*100.00%*	*87.48%*	*7.93%*	*4.59%*	*100.00%*
	65.95%	***45.61%***	***52.50%***	***25.85%***	***38.96%***	***54.16%***	***41.83%***	***43.08%***	***43.63%***	***40.02%***	***38.89%***	***43.08%***
Male	414	1,976	17,063	327	59,987	1,759	1,745	83,271	72,006	7,569	3,696	83,271
	0.28%	**1.34%**	**11.54%**	**0.22%**	**40.56%**	**1.19%**	**1.18%**	**56.31%**	**48.69%**	**5.12%**	**2.50%**	**56.31%**
	0.50%	*2.37%*	*20.49%*	*0.39%*	*72.04%*	*2.11%*	2.10%	*100.00%*	*86.47%*	*9.09%*	*4.44%*	*100.00%*
	34.05%	***54.39%***	***47.49%***	***74.15%***	***61.02%***	***45.84%***	***38.56%***	***56.31%***	***56.36%***	***59.97%***	***49.16%***	***56.31%***
Unknown	0	0	2	0	16	0	888	906	7	1	898	906
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	***0.60%***	**0.61%**	**0.00%**	**0.00%**	**0.61%**	**0.61%**
	0.00%	*0.00%*	0.22%	*0.00%*	*1.77%*	*0.00%*	*98.01%*	*100.00%*	*0.77%*	*0.11%*	*99.12%*	*100.00%*
	0.00%	***0.00%***	***0.01%***	***0.00%***	***0.02%***	***0.00%***	***19.62%***	***0.61%***	***0.01%***	***0.01%***	***11.94%***	***0.61%***
Total	1,216	3,633	35,930	441	98,307	3,837	4,526	147,890	127,751	12,621	7,518	147,890
	0.82%	**2.46%**	**24.30%**	**0.30%**	**66.47%**	**2.59%**	**3.06%**	**100.00%**	**86.38%**	**8.53%**	**5.08%**	**100.00%**
	0.82%	*2.46%*	*24.30%*	*0.30%*	*66.47%*	*2.59%*	*3.06%*	*100.00%*	*86.38%*	*8.53%*	*5.08%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form							
TOTAL		TOTAL		TOTAL		OVERALL	
Females	269,715	Males	211,532	Unknown	1,078	Total	482,325
	55.92%		43.86%		0.22%		100%

Total Number of Protocols with Enrollment Data: 539

Table 18: Aggregate Enrollment Data for Extramural Phase III Protocols, Excluding Male-Only and Female-Only Protocols Reported in FY2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	330	1,359	13,121	8,366	42,839	1,492	67,507
	0.23%	**0.97%**	**9.34%**	**5.95%**	**30.48%**	**1.06%**	**48.04%**
	0.49%	*2.01%*	*19.44%*	*12.39%*	*63.46%*	*2.21%*	*100.00%*
	48.53%	***49.71%***	***53.68%***	***53.60%***	***45.83%***	***41.57%***	***48.04%***
Male	349	1,375	11,321	7,160	50,629	2,015	72,849
	0.25%	**0.98%**	**8.06%**	**5.10%**	**36.03%**	**1.43%**	**51.84%**
	0.48%	*1.89%*	*15.54%*	*9.83%*	*69.50%*	*2.77%*	*100.00%*
	51.32%	***50.29%***	***46.32%***	***45.87%***	***54.16%***	***56.14%***	***51.84%***
Unknown	1	0	1	83	5	82	172
	0.001%	**0.00%**	**0.00%**	**0.06%**	**0.00%**	**0.06%**	**0.12%**
	0.58%	*0.00%*	*0.58%*	*48.26%*	*2.91%*	*47.67%*	*100.00%*
	0.15%	***0.00%***	***0.00%***	***0.53%***	***0.01%***	***2.28%***	***0.12%***
Total	680	2,734	24,443	15,609	93,473	3,589	140,528
	0.48%	**1.95%**	**17.39%**	**11.11%**	**66.52%**	**2.55%**	**100.00%**
	0.48%	*1.95%*	*17.39%*	*11.11%*	*66.52%*	*2.55%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 186

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 831 protocols of which 147 were *female-only* protocols and 31 were *male-only* protocols. Excluding sex-specific studies, the number of females (109,567 or 44%) to males (138,811 or 56%) enrolled in extramural research protocols are closely representative of the general population.

Largest identified racial group is Whites at 66.5% following the 1977 OMB standards and 63.4% following the 1997 OMB standards.

Largest identified racial minority group is Blacks at 17.4% following the 1977 OMB standards and 28.1% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives (0.5%).

According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.4%).

9% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 11% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 175

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown /Not Reported	Total
Female	466	814	14,948	86	23,295	1,485	966	42,060	36,540	2,799	2,721	42,060
	0.43%	**0.75%**	**13.72%**	**0.08%**	**21.39%**	**1.36%**	**0.89%**	**38.61%**	**33.55%**	**2.57%**	**2.50%**	**38.61%**
	1.11%	*1.94%*	*35.54%*	*0.20%*	*55.39%*	*3.53%*	*2.30%*	*100.00%*	*86.88%*	*6.65%*	*6.47%*	*100.00%*
	53.94%	***40.32%***	***48.73%***	***20.92%***	***33.75%***	***48.51%***	***33.64%***	***38.61%***	***39.64%***	***28.36%***	***39.53%***	***38.61%***
Male	398	1,205	15,729	323	45,713	1,576	1,018	65,962	55,630	7,068	3,264	65,962
	0.37%	**1.11%**	**14.44%**	**0.30%**	**41.97%**	**1.45%**	**0.93%**	**60.56%**	**51.07%**	**6.49%**	**3.00%**	**60.56%**
	0.60%	*1.83%*	*23.85%*	*0.49%*	*69.30%*	*2.39%*	1.54%	*100.00%*	*84.34%*	*10.72%*	*4.95%*	*100.00%*
	46.06%	***59.68%***	***51.27%***	***78.59%***	***66.23%***	***51.49%***	***35.45%***	***60.56%***	***60.35%***	***71.63%***	***47.42%***	***60.56%***
Unknown	0	0	0	2	16	0	888	906	7	1	898	906
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.01%**	**0.00%**	***0.82%***	**0.83%**	**0.01%**	**0.00%**	**0.82%**	**0.83%**
	0.00%	*0.00%*	0.00%	*0.22%*	*1.77%*	*0.00%*	*98.01%*	*100.00%*	*0.77%*	*0.11%*	*99.12%*	*100.00%*
	0.00%	***0.00%***	***0.00%***	***0.49%***	***0.02%***	***0.00%***	***30.92%***	***0.83%***	***0.01%***	***0.01%***	***13.05%***	***0.83%***
Total	864	2,019	30,677	411	69,024	3,061	2,872	108,928	92,177	9,868	6,883	108,928
	0.79%	**1.85%**	**28.16%**	**0.38%**	**63.37%**	**2.81%**	**2.64%**	**100.00%**	**84.62%**	**9.06%**	**6.32%**	**100.00%**
	0.79%	*1.85%*	*28.16%*	*0.38%*	*63.37%*	*2.81%*	*2.64%*	*100.00%*	*84.62%*	*9.06%*	*6.32%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form							
TOTAL		TOTAL		TOTAL		OVERALL	
Females	109,567	Males	138,811	Unknown	1,078	Total	249,456
	43.92%		55.65%		0.43%		100%

Total Number of Protocols with Enrollment Data: 361

Table 19. Aggregate Enrollment Data for Intramural Research Protocols Reported in FY 2003: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	9,511	128,639	52,418	35,421	585,064	57,453	868,506
	0.52%	**7.03%**	**2.86%**	**1.93%**	**31.95%**	**3.14%**	**47.43%**
	1.10%	*14.81%*	*6.04%*	*4.08%*	*67.36%*	*6.62%*	*100.00%*
	51.67%	***66.93%***	***50.71%***	***60.71%***	***43.99%***	***44.65%***	***47.43%***
Male	8,896	63,520	50,943	22,725	744,033	57,058	947,175
	0.49%	**3.47%**	**2.78%**	**1.24%**	**40.64%**	**3.12%**	**51.73%**
	0.94%	*6.71%*	*5.38%*	*2.40%*	*78.55%*	*6.02%*	*100.00%*
	48.33%	***33.05%***	***49.28%***	***38.95%***	***55.94%***	***44.34%***	***51.73%***
Unknown	0	41	10	200	870	14,165	15,286
	0.000%	**0.00%**	**0.00%**	**0.01%**	**0.05%**	**0.77%**	**0.83%**
	0.00%	*0.27%*	*0.07%*	*1.31%*	*5.69%*	*92.67%*	*100.00%*
	0.00%	***0.02%***	***0.01%***	***0.34%***	***0.07%***	***11.01%***	***0.83%***
Total	18,407	192,200	103,371	58,346	1,329,967	128,676	1,830,967
	1.01%	**10.50%**	**5.65%**	**3.19%**	**72.64%**	**7.03%**	**100.00%**
	1.01%	*10.50%*	*5.65%*	*3.19%*	*72.64%*	*7.03%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 1,199

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were more males (947,748 or 51.7%) than females (870,030 or 47.5%) enrolled in aggregate intramural research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (e.g. ensuring sex/gender declaration and recording at enrollment.
According to the 1977 OMB standards, the largest identified racial minority group is Asian/Pacific Islanders at (10.5%).
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives (1.01%).
According to the 1997 OMB standards, the largest identified racial minority group is Blacks at (17.3%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.03%).
5.3% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 3.2% of participants identified as Hispanics according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 156

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	2	75	312	1	1,024	3	107	1,524	1,388	99	37	1,524
	0.06%	**2.42%**	**10.07%**	**0.03%**	**33.06%**	**0.10%**	**3.45%**	**49.21%**	**44.82%**	**3.20%**	**1.19%**	**49.21%**
	0.13%	*4.92%*	*20.47%*	*0.07%*	*67.19%*	*0.20%*	*7.02%*	*100.00%*	*91.08%*	*6.50%*	*2.43%*	*100.00%*
	16.67%	***41.67%***	***58.10%***	***100.00%***	***46.86%***	***50.00%***	***60.80%***	***49.21%***	***48.28%***	***60.74%***	***62.71%***	***49.21%***
Male	10	105	225	0	1,161	3	69	1,573	1,487	64	22	1,573
	0.32%	**3.39%**	**7.27%**	**0.00%**	**37.49%**	**0.10%**	**2.23%**	**50.79%**	**48.01%**	**2.07%**	**0.71%**	**50.79%**
	0.64%	*6.68%*	*14.30%*	*0.00%*	*73.81%*	*0.19%*	4.39%	*100.00%*	*94.53%*	*4.07%*	*1.40%*	*100.00%*
	83.33%	***58.33%***	***41.90%***	***0.00%***	***53.14%***	***50.00%***	***39.20%***	***50.79%***	***51.72%***	***39.26%***	***37.29%***	***50.79%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	12	180	537	1	2,185	6	176	3,097	2,875	163	59	3,097
	0.39%	**5.81%**	**17.34%**	**0.03%**	**70.55%**	**0.19%**	**5.68%**	**100.00%**	**92.83%**	**5.26%**	**1.91%**	**100.00%**
	0.39%	*5.81%*	*17.34%*	*0.03%*	*70.55%*	*0.19%*	*5.68%*	*100.00%*	*92.83%*	*5.26%*	*1.91%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

TOTAL		TOTAL		TOTAL		OVERALL	
Females	870,030	Males	948,748	Unknown	15,286	Total	1,834,064
	47.44%		51.73%		0.83%		100%

Total Number of Protocols with Enrollment Data: 1,355

Table 20: Aggregate Enrollment Data for Intramural Research Protocols Excluding Male-Only and Female-Only Protocols Reported in FY2003

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	5	5910	222	118	2730	3439	12,424
	0.02%	**22.94%**	**0.86%**	**0.46%**	**10.60%**	**13.35%**	**48.22%**
	0.04%	*47.57%*	*1.79%*	*0.95%*	*21.97%*	*27.68%*	*100.00%*
	38.46%	***48.63%***	***48.79%***	***47.39%***	***44.99%***	***50.39%***	***48.22%***
Male	8	6244	233	131	3338	3386	13,340
	0.03%	**24.24%**	**0.90%**	**0.51%**	**12.96%**	**13.14%**	**51.78%**
	0.06%	*46.81%*	*1.75%*	*0.98%*	*25.02%*	*25.38%*	*100.00%*
	61.54%	***51.37%***	***51.21%***	***52.61%***	***55.01%***	***49.61%***	***51.78%***
Unknown	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	13	12,154	455	249	6,068	6,825	25,764
	0.05%	**47.17%**	**1.77%**	**0.97%**	**23.55%**	**26.49%**	**100.00%**
	0.05%	*47.17%*	*1.77%*	*0.97%*	*23.55%*	*26.49%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 1,021

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 1,355 protocols of which 124 were *female-only* protocols and 95 were *male-only* protocols.
Excluding sex-specific studies, the number of females (13,823 or 48.4%) to males (14,768 or 51.6%) enrolled in intramural research protocols are closely representative of the general population.
Largest identified racial group is White at 23.5% following the 1977 OMB standards and 69.7% following the 1997 OMB standards.
Largest identified racial minority group is Asian/Pacific Islanders at 47.2% following the 1977 OMB standards.
Largest identified racial minority group is Blacks at 18.1% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.05%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.04%).
5.2% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards, whereas 0.97% of participants identified as Hispanic according to 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 115

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	2	72	301	1	921	3	99	1,399	1,275	88	36	1,399
	0.07%	**2.55%**	**10.65%**	**0.04%**	**32.58%**	**0.11%**	**3.50%**	**49.49%**	**45.10%**	**3.11%**	**1.27%**	**49.49%**
	0.14%	*5.15%*	*21.52%*	*0.07%*	*65.83%*	*0.21%*	*7.08%*	*100.00%*	*91.14%*	*6.29%*	*2.57%*	*100.00%*
	22.22%	***42.86%***	***58.90%***	***100.00%***	***46.70%***	***50.00%***	***61.88%***	***49.49%***	***48.55%***	***60.69%***	***64.29%***	***49.49%***
Male	7	96	210	0	1,051	3	61	1,428	1,351	57	20	1,428
	0.25%	**3.40%**	**7.43%**	**0.00%**	**37.18%**	**0.11%**	**2.16%**	**50.51%**	**47.79%**	**2.02%**	**0.71%**	**50.51%**
	0.49%	*6.72%*	*14.71%*	*0.00%*	*73.60%*	*0.21%*	*4.27%*	*100.00%*	*94.61%*	*3.99%*	*1.40%*	*100.00%*
	77.78%	***57.14%***	***41.10%***	***0.00%***	***53.30%***	***50.00%***	***38.13%***	***50.51%***	***51.45%***	***39.31%***	***35.71%***	***50.51%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	9	168	511	1	1,972	6	160	2,827	2,626	145	56	2,827
	0.32%	**5.94%**	**18.08%**	**0.04%**	**69.76%**	**0.21%**	**5.66%**	**100.00%**	**92.89%**	**5.13%**	**1.98%**	**100.00%**
	0.32%	*5.94%*	*18.08%*	*0.04%*	*69.76%*	*0.21%*	*5.66%*	*100.00%*	*92.89%*	*5.13%*	*1.98%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	13,823	Males	14,768	Unknown	0	Total	28,591
	48.35%		51.65%		0.00%		100%

Total Number of Protocols with Enrollment Data: 1,136

Table 21. Aggregate Enrollment Data for Intramural Research Protocols Reported in FY 2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	9,537	131,618	54,306	50,267	599,553	53,061	898,342
	0.51%	6.99%	2.88%	2.67%	31.84%	2.82%	47.71%
	1.06%	*14.65%*	*6.05%*	*5.60%*	*66.74%*	*5.91%*	*100.00%*
	51.40%	***66.78%***	***51.42%***	***66.88%***	***44.20%***	***40.82%***	***47.71%***
Male	8,994	65,419	51,286	24,583	754,327	66,892	971,501
	0.48%	3.47%	2.72%	1.31%	40.06%	3.55%	51.59%
	0.93%	*6.73%*	*5.28%*	*2.53%*	*77.65%*	*6.89%*	*100.00%*
	48.47%	***33.19%***	***48.56%***	***32.71%***	***55.60%***	***51.46%***	***51.59%***
Unknown	23	41	16	308	2,724	10,036	13,148
	0.001%	0.00%	0.00%	0.02%	0.14%	0.53%	0.70%
	0.17%	*0.31%*	*0.12%*	*2.34%*	*20.72%*	*76.33%*	*100.00%*
	0.12%	***0.02%***	***0.02%***	***0.41%***	***0.20%***	***7.72%***	***0.70%***
Total	18,554	197,078	105,608	75,158	1,356,604	129,989	1,882,991
	0.99%	10.47%	5.61%	3.99%	72.05%	6.90%	100.00%
	0.99%	*10.47%*	*5.61%*	*3.99%*	*72.05%*	*6.90%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 951

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were more males (986,964 or 50.7%) than females (943,116 or 48.4%) enrolled in aggregate intramural research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (e.g. ensuring sex/gender declaration and recording at enrollment.
According to the 1977 OMB standards, the largest identified racial minority group is Asian Pacific Islanders at (10.47%).
According to the 1997 OMB standards, the largest identified racial minority group is Blacks at (9.14%).
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (0.1%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islander at (0.01%).
2.8% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 4% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 440

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	545	1,173	3,130	2	38,286	8	1,630	44,774	43,487	1,156	131	44,774
	0.85%	1.83%	4.88%	0.00%	59.63%	0.01%	2.54%	69.74%	67.74%	1.80%	0.20%	69.74%
	1.22%	*2.62%*	*6.99%*	*0.00%*	*85.51%*	*0.02%*	*3.64%*	*100.00%*	*97.13%*	*2.58%*	*0.29%*	*100.00%*
	76.33%	***43.97%***	***53.35%***	***50.00%***	***75.79%***	***6.15%***	***37.90%***	***69.74%***	***70.78%***	***63.73%***	***13.83%***	***69.74%***
Male	169	1,012	2,456	2	11,074	12	738	15,463	14,919	454	90	15,463
	0.26%	1.58%	3.83%	0.00%	17.25%	0.02%	1.15%	24.09%	23.24%	0.71%	0.14%	24.09%
	1.09%	*6.54%*	*15.88%*	*0.01%*	*71.62%*	*0.08%*	*4.77%*	*100.00%*	*96.48%*	*2.94%*	*0.58%*	*100.00%*
	23.67%	***37.93%***	***41.86%***	***50.00%***	***21.92%***	***9.23%***	***17.16%***	***24.09%***	***24.28%***	***25.03%***	***9.50%***	***24.09%***
Unknown	0	483	281	0	1,157	110	1,933	3,964	3,034	204	726	3,964
	0.00%	0.75%	0.44%	0.00%	1.80%	0.17%	*3.01%*	6.17%	4.73%	0.32%	1.13%	6.17%
	0.00%	*12.18%*	*7.09%*	0.00%	*29.19%*	*2.77%*	*48.76%*	*100.00%*	*76.54%*	*5.15%*	*18.31%*	*100.00%*
	0.00%	***18.10%***	***4.79%***	***0.00%***	***2.29%***	***84.62%***	***44.94%***	***6.17%***	***4.94%***	***11.25%***	***76.66%***	***6.17%***
Total	714	2,668	5,867	4	50,517	130	4,301	64,201	61,440	1,814	947	64,201
	1.11%	4.16%	9.14%	0.01%	78.69%	0.20%	6.70%	100.00%	95.70%	2.83%	1.48%	100.00%
	1.11%	*4.16%*	*9.14%*	*0.01%*	*78.69%*	*0.20%*	*6.70%*	*100.00%*	*95.70%*	*2.83%*	*1.48%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	943,116	Males	986,964	Unknown	28,611	Total	1,947,192
	48.43%		50.69%		1.47%		100%

Total Number of Protocols with Enrollment Data: 1,391

Table 22: Aggregate Enrollment Data for Intramural Research Protocols Excluding Male-Only and Female-Only Protocols Reported in FY2004

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	9,259	53,482	45,637	18,354	496,634	45,115	668,481
	0.58%	**3.34%**	**2.85%**	**1.15%**	**30.98%**	**2.81%**	**41.70%**
	1.39%	*8.00%*	*6.83%*	*2.75%*	*74.29%*	*6.75%*	*100.00%*
	50.68%	***45.01%***	***47.55%***	***42.46%***	***40.48%***	***45.29%***	***41.70%***
Male	8,989	65,290	50,322	24,566	727,639	44,455	921,261
	0.56%	**4.07%**	**3.14%**	**1.53%**	**45.40%**	**2.77%**	**57.47%**
	0.98%	*7.09%*	*5.46%*	*2.67%*	*78.98%*	*4.83%*	*100.00%*
	49.20%	***54.95%***	***52.43%***	***56.83%***	***59.30%***	***44.63%***	***57.47%***
Unknown	23	41	16	308	2,724	10,036	13,148
	0.001%	**0.00%**	**0.00%**	**0.02%**	**0.17%**	**0.63%**	**0.82%**
	0.17%	*0.31%*	*0.12%*	*2.34%*	*20.72%*	*76.33%*	*100.00%*
	0.13%	***0.03%***	***0.02%***	***0.71%***	***0.22%***	***10.08%***	***0.82%***
Total	18,271	118,813	95,975	43,228	1,226,997	99,606	1,602,890
	1.14%	**7.41%**	**5.99%**	**2.70%**	**76.55%**	**6.21%**	**100.00%**
	1.14%	*7.41%*	*5.99%*	*2.70%*	*76.55%*	*6.21%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 823

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were 1,391 protocols of which 133 were *female-only* protocols and 86 were *male-only* protocols. Excluding sex-specific studies, the number of females (683,807 or 41.8%) to males (935,883 or 57.2%) enrolled in intramural research protocols are closely representative of the general population.

Largest identified racial group is White at 76.5% following the 1977 OMB standards and 66.4% following the 1997 OMB standards.

Largest identified racial minority group is Asian/Pacific Islanders at 16% following the 1977 OMB standards.

Largest identified racial minority group is Blacks at 15.8% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives at (1.14%).

According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.01%).

2.8% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards, whereas 2.7% of participants identified as Hispanic according to 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 349

	Total of All Subjects by Race								Total of All Subjects by Ethnicities			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	375	898	2,693	2	10,824	8	526	15,326	14,831	370	125	15,326
	1.11%	**2.65%**	**7.94%**	**0.01%**	**31.92%**	**0.02%**	**1.55%**	**45.19%**	**43.73%**	**1.09%**	**0.37%**	**45.19%**
	2.45%	*5.86%*	*17.57%*	*0.01%*	*70.63%*	*0.05%*	*3.43%*	*100.00%*	*96.77%*	*2.41%*	*0.82%*	*100.00%*
	68.93%	***37.70%***	***50.21%***	***66.67%***	***48.10%***	***6.15%***	***17.63%***	***45.19%***	***46.33%***	***38.38%***	***13.37%***	***45.19%***
Male	169	1,001	2,390	1	10,524	12	525	14,622	14,148	390	84	14,622
	0.50%	**2.95%**	**7.05%**	**0.00%**	**31.03%**	**0.04%**	**1.55%**	**43.12%**	**41.72%**	**1.15%**	**0.25%**	**43.12%**
	1.16%	*6.85%*	*16.35%*	*0.01%*	*71.97%*	*0.08%*	3.59%	*100.00%*	*96.76%*	*2.67%*	*0.57%*	*100.00%*
	31.07%	***42.02%***	***44.56%***	***33.33%***	***46.76%***	***9.23%***	***17.59%***	***43.12%***	***44.19%***	***40.46%***	***8.98%***	***43.12%***
Unknown	0	483	281	0	1,157	110	1,933	3,964	3,034	204	726	3,964
	0.00%	**1.42%**	**0.83%**	**0.00%**	**3.41%**	**0.32%**	***5.70%***	**11.69%**	**8.95%**	**0.60%**	**2.14%**	**11.69%**
	0.00%	*12.18%*	*7.09%*	0.00%	*29.19%*	*2.77%*	*48.76%*	*100.00%*	*76.54%*	*5.15%*	*18.31%*	*100.00%*
	0.00%	***20.28%***	***5.24%***	***0.00%***	***5.14%***	***84.62%***	***64.78%***	***11.69%***	***9.48%***	***21.16%***	***77.65%***	***11.69%***
Total	544	2,382	5,364	3	22,505	130	2,984	33,912	32,013	964	935	33,912
	1.60%	**7.02%**	**15.82%**	**0.01%**	**66.36%**	**0.38%**	**8.80%**	**100.00%**	**94.40%**	**2.84%**	**2.76%**	**100.00%**
	1.60%	*7.02%*	*15.82%*	*0.01%*	*66.36%*	*0.38%*	*8.80%*	*100.00%*	*94.40%*	*2.84%*	*2.76%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	683,807	Males	935,883	Unknown	17,112	Total	1,636,802
	41.78%		57.18%		1.05%		100%

Total Number of Protocols with Enrollment Data: 1,172

Table 23. Aggregate Enrollment for Intramural Phase III Research Protocols Reported in FY 2003: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	5	5910	222	118	2730	3439	12,424
	0.02%	**22.94%**	**0.86%**	**0.46%**	**10.60%**	**13.35%**	**48.22%**
	0.04%	*47.57%*	*1.79%*	*0.95%*	*21.97%*	*27.68%*	*100.00%*
	38.46%	***48.63%***	***48.79%***	***47.39%***	***44.99%***	***50.39%***	***48.22%***
Male	8	6244	233	131	3338	3386	13,340
	0.03%	**24.24%**	**0.90%**	**0.51%**	**12.96%**	**13.14%**	**51.78%**
	0.06%	*46.81%*	*1.75%*	*0.98%*	*25.02%*	*25.38%*	*100.00%*
	61.54%	***51.37%***	***51.21%***	***52.61%***	***55.01%***	***49.61%***	***51.78%***
Unknown	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	13	12,154	455	249	6,068	6,825	25,764
	0.05%	**47.17%**	**1.77%**	**0.97%**	**23.55%**	**26.49%**	**100.00%**
	0.05%	*47.17%*	*1.77%*	*0.97%*	*23.55%*	*26.49%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 29

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were more males (13,430 or 51.6%) than females (12,589 or 48.3%) enrolled in aggregate intramural research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (e.g. ensuring sex/gender declaration and recording at enrollment.
According to the 1977 OMB standards, the largest identified racial minority group is Asian and Pacific Islanders at (47.17%).
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Native (0.05%).
According to the 1997 OMB standards, the largest identified racial minority group is Blacks at (34.9%).
According to the 1997 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Native (0%).
4.71% of participants identified their ethnicity as Hispanic or Latino, following the 1997 OMB standards wheras 0.97% of participants identified as Hispanic or Latino.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 4

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	0	2	70	1	80	1	11	165	153	8	4	165
	0.00%	**0.78%**	**27.45%**	**0.39%**	**31.37%**	**0.39%**	**4.31%**	**64.71%**	**60.00%**	**3.14%**	**1.57%**	**64.71%**
	0.00%	*1.21%*	*42.42%*	*0.61%*	*48.48%*	*0.61%*	*6.67%*	*100.00%*	*92.73%*	*4.85%*	*2.42%*	*100.00%*
	0.00%	***28.57%***	***78.65%***	***100.00%***	***56.74%***	***100.00%***	***68.75%***	***64.71%***	***64.29%***	***66.67%***	***80.00%***	***64.71%***
Male	0	5	19	0	61	0	5	90	85	4	1	90
	0.00%	**1.96%**	**7.45%**	**0.00%**	**23.92%**	**0.00%**	**1.96%**	**35.29%**	**33.33%**	**1.57%**	**0.39%**	**35.29%**
	0.00%	*5.56%*	*21.11%*	*0.00%*	*67.78%*	*0.00%*	5.56%	*100.00%*	*94.44%*	*4.44%*	*1.11%*	*100.00%*
	0.00%	***71.43%***	***21.35%***	***0.00%***	***43.26%***	***0.00%***	***31.25%***	***35.29%***	***35.71%***	***33.33%***	***20.00%***	***35.29%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	0	7	89	1	141	1	16	255	238	12	5	255
	0.00%	**2.75%**	**34.90%**	**0.39%**	**55.29%**	**0.39%**	**6.27%**	**100.00%**	**93.33%**	**4.71%**	**1.96%**	**100.00%**
	0.00%	*2.75%*	*34.90%*	*0.39%*	*55.29%*	*0.39%*	*6.27%*	*100.00%*	*93.33%*	*4.71%*	*1.96%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL	OVERALL	
Females	12,589	Males	13,430	Unknown	0	Total	26,019
	48.38%		51.62%		0.00%		100%

Total Number of Protocols with Enrollment Data: 33

Table 24: Aggregate Enrollment Data for Intramural Phase III Protocols, Excluding Male-Only and Female-Only Protocols Reported in FY2003:

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	5	5,910	222	118	2,730	3,439	12,424
	0.02%	**22.96%**	**0.86%**	**0.46%**	**10.61%**	**13.36%**	**48.26%**
	0.04%	*47.57%*	*1.79%*	*0.95%*	*21.97%*	*27.68%*	*100.00%*
	41.67%		***49.22%***	***47.39%***	***45.10%***	***50.39%***	***48.26%***
Male	7	6,242	229	131	3,322	3,386	13,317
	0.03%	**24.25%**	**0.89%**	**0.51%**	**12.90%**	**13.15%**	**51.73%**
	0.05%	*46.87%*	*1.72%*	*0.98%*	*24.95%*	*25.43%*	*100.00%*
	58.33%	***51.37%***	***50.78%***	***52.61%***	***54.88%***	***49.61%***	***51.73%***
Unknown	0	0	0	0	1	0	1
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*100.00%*	*0.00%*	*100.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.02%***	***0.00%***	***0.00%***
Total	12	12,152	451	249	6,053	6,825	25,742
	0.05%	**47.21%**	**1.75%**	**0.97%**	**23.51%**	**26.51%**	**100.00%**
	0.05%	*47.21%*	*1.75%*	*0.97%*	*23.51%*	*26.51%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 28

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

Excluding sex-specific studies, the number of females (12,589 or 48.4%) to males (13,396 or 51.5%) enrolled in intramural research protocols are closely representative of the general population.

Largest identified racial group is Whites at 23.5% following the 1977 OMB standards and 53.7% following the 1997 OMB standards.

Largest identified racial minority group is Asian/Pacific Islanders at 47.2% following the 1977 OMB standards.

Largest identified racial minority group is Black at 36.5% following the 1997 OMB standards.

According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives (0.05%) and 0% following the 1997 OMB standards.

4.51% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 0.97% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 2

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	0	2	70	1	80	1	11	165	153	8	4	165
	0.00%	**0.82%**	**28.69%**	**0.41%**	**32.79%**	**0.41%**	**4.51%**	**67.62%**	**62.70%**	**3.28%**	**1.64%**	**67.62%**
	0.00%	*1.21%*	*42.42%*	*0.61%*	*48.48%*	*0.61%*	*6.67%*	*100.00%*	*92.73%*	*4.85%*	*2.42%*	*100.00%*
	0.00%	***28.57%***	***78.65%***	***100.00%***	***61.07%***	***100.00%***	***73.33%***	***67.62%***	***67.11%***	***72.73%***	***80.00%***	***67.62%***
Male	0	5	19	0	51	0	4	79	75	3	1	79
	0.00%	**2.05%**	**7.79%**	**0.00%**	**20.90%**	**0.00%**	**1.64%**	**32.38%**	**30.74%**	**1.23%**	**0.41%**	**32.38%**
	0.00%	*6.33%*	*24.05%*	*0.00%*	*64.56%*	*0.00%*	5.06%	*100.00%*	*94.94%*	*3.80%*	*1.27%*	*100.00%*
	0.00%	***71.43%***	***21.35%***	***0.00%***	***38.93%***	***0.00%***	***26.67%***	***32.38%***	***32.89%***	***27.27%***	***20.00%***	***32.38%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	0	7	89	1	131	1	15	244	228	11	5	244
	0.00%	**2.87%**	**36.48%**	**0.41%**	**53.69%**	**0.41%**	**6.15%**	**100.00%**	**93.44%**	**4.51%**	**2.05%**	**100.00%**
	0.00%	*2.87%*	*36.48%*	*0.41%*	*53.69%*	*0.41%*	*6.15%*	*100.00%*	*93.44%*	*4.51%*	*2.05%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL	
Females	12,589	Males	13,396	Unknown	1	Total	25,986
	48.45%		51.55%		0.00%		100%

Total Number of Protocols with Enrollment Data: 30

Table 25. Intramural Phase III Research Protocols Reported in FY 2004: Percent Analysis

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	9	5966	364	4948	1449	3919	16,655
	0.03%	**17.88%**	**1.09%**	**14.83%**	**4.34%**	**11.74%**	**49.90%**
	0.05%	*35.82%*	*2.19%*	*29.71%*	*8.70%*	*23.53%*	*100.00%*
	37.50%	***48.65%***	***50.70%***	***56.68%***	***37.94%***	***50.10%***	***49.90%***
Male	15	6296	354	3781	2370	3903	16,719
	0.04%	**18.86%**	**1.06%**	**11.33%**	**7.10%**	**11.69%**	**50.10%**
	0.09%	*37.66%*	*2.12%*	*22.61%*	*14.18%*	*23.34%*	*100.00%*
	62.50%	***51.35%***	***49.30%***	***43.32%***	***62.06%***	***49.90%***	***50.10%***
Unknown	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	24	12,262	718	8,729	3,819	7,822	33,374
	0.07%	**36.74%**	**2.15%**	**26.16%**	**11.44%**	**23.44%**	**100.00%**
	0.07%	*36.74%*	*2.15%*	*26.16%*	*11.44%*	*23.44%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 25

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

There were more females (17,086 or 50.2%) than males (16,949 or 49.8%) enrolled in aggregate intramural research protocols.
Differences in the enrollment of males and females is attributed primarily to improvements in reporting procedures (e.g. ensuring sex/gender declaration and recording at enrollment.
According to the 1977 OMB standards, the largest identified racial minority group is Asian Pacific Islander at (36.74%).
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Native (0.07%).
According to the 1997 OMB standards, the largest identified racial minority group is Blacks at (31.2%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islander at (0.15%).
4.4% of participants identified their ethnicity as Hispanic or Latino. Whereas 26% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 12

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	2	4	162	1	233	1	28	431	401	21	9	431
	0.30%	**0.61%**	**24.51%**	**0.15%**	**35.25%**	**0.15%**	**4.24%**	**65.20%**	**60.67%**	**3.18%**	**1.36%**	**65.20%**
	0.46%	*0.93%*	*37.59%*	*0.23%*	*54.06%*	*0.23%*	*6.50%*	*100.00%*	*93.04%*	*4.87%*	*2.09%*	*100.00%*
	66.67%	***28.57%***	***78.64%***	***100.00%***	***58.84%***	***50.00%***	***71.79%***	***65.20%***	***64.78%***	***72.41%***	***69.23%***	***65.20%***
Male	1	10	44	0	163	1	11	230	218	8	4	230
	0.15%	**1.51%**	**6.66%**	**0.00%**	**24.66%**	**0.15%**	**1.66%**	**34.80%**	**32.98%**	**1.21%**	**0.61%**	**34.80%**
	0.43%	*4.35%*	*19.13%*	*0.00%*	*70.87%*	*0.43%*	*4.78%*	*100.00%*	*94.78%*	*3.48%*	*1.74%*	*100.00%*
	33.33%	***71.43%***	***21.36%***	***0.00%***	***41.16%***	***50.00%***	***28.21%***	***34.80%***	***35.22%***	***27.59%***	***30.77%***	***34.80%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	3	14	206	1	396	2	39	661	619	29	13	661
	0.45%	**2.12%**	**31.16%**	**0.15%**	**59.91%**	**0.30%**	**5.90%**	**100.00%**	**93.65%**	**4.39%**	**1.97%**	**100.00%**
	0.45%	*2.12%*	*31.16%*	*0.15%*	*59.91%*	*0.30%*	*5.90%*	*100.00%*	*93.65%*	*4.39%*	*1.97%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form

TOTAL		TOTAL		TOTAL		OVERALL
Females	17,086	Males	16,949	Unknown	0	Total 34,035
	50.20%		49.80%		0.00%	100%

Total Number of Protocols with Enrollment Data: 37

Table 26: Aggregate Enrollment Data for Intramural Phase III Protocols, Excluding Male-Only and Female-Only Protocols Reported in FY2004:

Old Form: Total of All Subjects Reported Using the 1977 OMB Standards

	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic	White	Unknown/ Other	Total
Female	9	5,966	364	4,948	1,449	3,919	16,655
	0.03%	**17.89%**	**1.09%**	**14.84%**	**4.34%**	**11.75%**	**49.94%**
	0.05%	*35.82%*	*2.19%*	*29.71%*	*8.70%*	*23.53%*	*100.00%*
	39.13%	***48.66%***	***50.98%***	***56.69%***	***38.11%***	***50.10%***	***49.94%***
Male	14	6,294	350	3,780	2,353	3,903	16,694
	0.04%	**18.87%**	**1.05%**	**11.33%**	**7.06%**	**11.70%**	**50.06%**
	0.08%	*37.70%*	*2.10%*	*22.64%*	*14.09%*	*23.38%*	*100.00%*
	60.87%	***51.34%***	***49.02%***	***43.31%***	***61.89%***	***49.90%***	***50.06%***
Unknown	0	0	0	0	0	0	0
	0.000%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*100.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	23	12,260	714	8,728	3,802	7,822	33,349
	0.07%	**36.76%**	**2.14%**	**26.17%**	**11.40%**	**23.45%**	**100.00%**
	0.07%	*36.76%*	*2.14%*	*26.17%*	*11.40%*	*23.45%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 24

Legend

Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Data Table Comments:

Excluding sex-specific studies, the number of females (17,086 or 50.3%) to males (16,908 or 49.7%) enrolled in intramural research protocols are closely representative of the general population.
Largest identified racial minority group is Asian/Pacific Islanders at 36.8% following the 1977 OMB standards.
Largest identified racial minority group is Blacks at 31.9% following the 1997 OMB standards.
According to the 1977 OMB standards, the smallest identified racial minority group is American Indian/Alaskan Natives (0.07%).
According to the 1997 OMB standards, the smallest identified racial minority group is Hawaiian/Pacific Islanders at (0.16%).
4.3% of participants identified their ethnicity as Hispanic or Latino following the 1997 OMB standards. Whereas, 26.2% of participants identified as Hispanic according to the 1977 OMB standards.

New Form: Total of All Subjects Reported Using the 1997 OMB Standards

Number of Protocols with Enrollment Data: 10

	Total of All Subjects by Race								Total of All Subjects by Ethnicity			
	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
Female	2	4	162	1	233	1	28	431	401	21	9	431
	0.31%	**0.62%**	**25.12%**	**0.16%**	**36.12%**	**0.16%**	**4.34%**	**66.82%**	**62.17%**	**3.26%**	**1.40%**	**66.82%**
	0.46%	*0.93%*	*37.59%*	*0.23%*	*54.06%*	*0.23%*	*6.50%*	*100.00%*	*93.04%*	*4.87%*	*2.09%*	*100.00%*
	66.67%	***28.57%***	***78.64%***	***100.00%***	***61.15%***	***50.00%***	***73.68%***	***66.82%***	***66.39%***	***75.00%***	***69.23%***	***66.82%***
Male	1	10	44	0	148	1	10	214	203	7	4	214
	0.16%	**1.55%**	**6.82%**	**0.00%**	**22.95%**	**0.16%**	**1.55%**	**33.18%**	**31.47%**	**1.09%**	**0.62%**	**33.18%**
	0.47%	*4.67%*	*20.56%*	*0.00%*	*69.16%*	*0.47%*	*4.67%*	*100.00%*	*94.86%*	*3.27%*	*1.87%*	*100.00%*
	33.33%	***71.43%***	***21.36%***	***0.00%***	***38.85%***	***50.00%***	***26.32%***	***33.18%***	***33.61%***	***25.00%***	***30.77%***	***33.18%***
Unknown	0	0	0	0	0	0	0	0	0	0	0	0
	0.00%	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**	***0.00%***	**0.00%**	**0.00%**	**0.00%**	**0.00%**	**0.00%**
	0.00%	0.00%	0.00%	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*	*0.00%*
	0.00%	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***	***0.00%***
Total	3	14	206	1	381	2	38	645	604	28	13	645
	0.47%	**2.17%**	**31.94%**	**0.16%**	**59.07%**	**0.31%**	**5.89%**	**100.00%**	**93.64%**	**4.34%**	**2.02%**	**100.00%**
	0.47%	*2.17%*	*31.94%*	*0.16%*	*59.07%*	*0.31%*	*5.89%*	*100.00%*	*93.64%*	*4.34%*	*2.02%*	*100.00%*
	100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

SUMMARY TOTALS: Old Form + New Form							
TOTAL		TOTAL		TOTAL		OVERALL	
Females	17,086	Males	16,908	Unknown	0	Total	33,994
	50.26%		49.74%		0.00%		100%

Total Number of Protocols with Enrollment Data: 34

Table 27. Summary Ethnicity Enrollment Report: Number of Hispanics or Latinos Reported in FY 2003 and FY 2004: Percent Analysis

Hispanic Ethnicity Enrollment by Sex and Race

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black or African American	White	Hawaiian/ Pacific Islander	More Than One Race	Unknown/ Other	TOTAL
2003	Female	2,902	1,326	7,949	224,153	311	14,460	127,507	378,608
	%	**0.47%**	**0.22%**	**1.30%**	**36.65%**	**0.00%**	**2.36%**	**20.85%**	**61.90%**
		0.77%	*0.35%*	*2.10%*	*59.20%*	*0.08%*	*3.82%*	*33.68%*	*100.00%*
		53.74%	***67.90%***	***54.57%***	***63.96%***	***45.80%***	***51.48%***	***60.57%***	***61.90%***
	Male	2,481	627	6,582	125,737	367	13,545	81,493	230,832
	%	**0.41%**	**0.10%**	**1.08%**	**20.56%**	**0.06%**	**2.21%**	**13.32%**	**37.74%**
		1.07%	*0.27%*	*2.85%*	*54.47%*	*0.16%*	*5.87%*	*35.30%*	*100.00%*
		45.94%	***32.10%***	***45.19%***	***35.88%***	***54.05%***	***48.22%***	***38.71%***	***37.74%***
	Unknown	17	0	35	549	1	83	1,516	2,201
	%	**0.00%**	**0.00%**	**0.01%**	**0.09%**	**0.00%**	**0.01%**	**0.25%**	**0.36%**
		0.77%	*0.00%*	*1.59%*	*24.94%*	*0.05%*	*3.77%*	*68.88%*	*100.00%*
		0.31%	***0.00%***	***0.24%***	***0.16%***	***0.15%***	***0.30%***	***0.72%***	***0.36%***
	TOTAL	5,400	1,953	14,566	350,439	679	28,088	210,516	611,641
	%	**0.88%**	**0.32%**	**2.38%**	**57.29%**	**0.11%**	**4.59%**	**34.42%**	**100.00%**
		0.88%	*0.32%*	*2.38%*	*57.29%*	*0.11%*	*4.59%*	*34.42%*	*100.00%*
		100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Legend
Bold: Percentage of Total No. of Participants in Research Protocols (Old or New Form)
Italics: Percentage of Total No. of Participants Sorted by Sex/Gender (Row Total)
Bold Italic: Percentage of Total No. of Participants sorted by Race/Ethnicity (Column Total)

Number of Protocols with Enrollment Data: 5,313

2004	Female	3635	2777	13372	238291	951	31611	182887	473,524
	%	**0.48%**	**0.37%**	**1.77%**	**31.51%**	**0.13%**	**4.18%**	**24.18%**	**62.61%**
		0.77%	*0.59%*	*2.82%*	*50.32%*	*0.20%*	*6.68%*	*38.62%*	*100.00%*
		56.73%	***55.10%***	***52.90%***	***65.99%***	***46.69%***	***50.25%***	***62.30%***	***62.61%***
	Male	2683	2105	11639	119401	891	30630	109094	276,443
	%	**0.35%**	**0.28%**	**1.54%**	**15.79%**	**0.12%**	**4.05%**	**14.42%**	**36.55%**
		0.97%	*0.76%*	*4.21%*	*43.19%*	*0.32%*	*11.08%*	*39.46%*	*100.00%*
		41.87%	***41.77%***	***46.05%***	***33.06%***	***43.74%***	***48.69%***	***37.16%***	***36.55%***
	Unknown	90	158	265	3420	195	668	1576	6,372
	%	**0.01%**	**0.02%**	**0.04%**	**0.45%**	**0.03%**	**0.09%**	**0.21%**	**0.84%**
		1.41%	*2.48%*	*4.16%*	*53.67%*	*3.06%*	*10.48%*	*24.73%*	*100.00%*
		1.40%	***3.13%***	***1.05%***	***0.95%***	***9.57%***	***1.06%***	***0.54%***	***0.84%***
	TOTAL	6,408	5,040	25,276	361,112	2,037	62,909	293,557	756,339
	%	**0.85%**	**0.67%**	**3.34%**	**47.74%**	**0.27%**	**8.32%**	**38.81%**	**100.00%**
		0.85%	*0.67%*	*3.34%*	*47.74%*	*0.27%*	*8.32%*	*38.81%*	*100.00%*
		100.00%	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***	***100.00%***

Number of Protocols with Enrollment Data: 7,343

SUMMARY TOTALS: Old Form + New Form								
2003	TOTAL				TOTAL		OVERALL	
	Females	378,608		230,832	Unknown	2,201	Total	611,641
		61.90%		37.74%		0.36%		100%
2004	TOTAL				TOTAL		OVERALL	
	Females	473,524		276,443	Unknown	6,372	Total	756,339
		62.61%		36.55%		0.84%		100%

protocols that continue to report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 12.9 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 7 percent, Asian/Pacific Islanders were 1.9 percent and whites (not Hispanic) 76 percent of the participants. The categories Hawaiian/Pacific Islander and More Than One Race were not designations with the 1977 OMB standards and, therefore, no data were reported in these categories. (Table 17)

In FY 2004, there were 266 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Accordingly, minority representation by race was highest for blacks at 24.3 percent and lowest for Hawaiian/Pacific Islanders 0.3 percent. Asians represented 2.46 percent, American Indian/Alaska Natives 0.8 percent and whites 66.5 percent of participants. Participants identifying More Than One Race were 2.6 percent of the total number of participants. Of the 266 extramural Phase III research protocols designating an ethnicity in FY 2004, 86.4 percent identified a racial category and an ethnicity of not Hispanic. Whereas, 8.5 percent identified a racial category and an ethnic category of Hispanic/Latino, 5 percent of participants identified a racial category, but did not report an ethnicity. (Table 17)

Intramural Research: FY 2003 and FY 2004

Substantial numbers of women and minorities were included in NIH intramural studies in FY 2003 and FY 2004. In FY 2003, approximately 1.8 million participants were reported in all intramural research including Phase III clinical trials, and other clinical studies. Approximately 47.5 percent were women, 51.7 percent were men, and 0.8 percent did not identify their sex. Of the 951 intramural research protocols that continue to report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 10.5 percent and lowest for American Indian/Alaska Natives at 1 percent. Blacks (not Hispanic) represented approximately 5.6 percent; Hispanics 3.2 percent; and whites (not Hispanic) 72.6 percent of the intramural research study population. The categories Hawaiian/Pacific Islander and More Than One Race were not designations with the 1977 OMB standards and, therefore, no data were reported in these categories. (Table 19)

For all intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2003, the largest racial minority group was Blacks at 17.3 percent and the smallest racial minority group was Hawaiian/Pacific Islanders at .03 percent. Asians represented 5.8 percent, American Indian/Alaska Natives 0.4 percent and whites 70.5 percent of participants in all intramural clinical research. Approximately 0.2 percent of participants reported More Than One Race as their racial category. Of the 156 intramural research protocols reporting data following the current 1997 OMB standards and designating an ethnicity in FY 2003, 92.8 percent identified a racial category and an ethnicity of not Hispanic. Whereas, 5.3 percent identified a racial category and an ethnic category of Hispanic/Latino, 1.9 percent of participants identified a racial category, but did not report an ethnicity. (Table 19)

In FY 2004, approximately 1.9 million participants were reported in all intramural research, including Phase III clinical trials and other clinical studies. Of the 951 intramural research protocols that continue to report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 10.5 percent and lowest for American Indian/Alaska Natives at 0.9 percent. Blacks (not Hispanic) represented 5.6 percent, Hispanics 4 percent; and whites (not Hispanic) 72 percent of the intramural research study population. The categories Hawaiian/Pacific Islander and More Than One Race were not designations with the 1977 OMB standards and, therefore, no data were reported in these categories. (Table 21)

For all intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2004, the largest racial minority group was blacks at 9.14 percent and the smallest racial minority group was Hawaiian/Pacific Islanders at .01 percent. Asians represented 4.2 percent, American Indian/Alaska Natives 1.1 percent, and

whites 78.7 percent of participants in all intramural clinical research. Approximately 0.2 percent of participants reported More Than One Race as their racial category. Of the 440 intramural research protocols following the current 1997 OMB standards designating an ethnicity in FY 2004, 95.7 percent identified a racial category and an ethnicity of not Hispanic. Whereas, 2.8 percent identified a racial category and an ethnic category of Hispanic/Latino, 1.5 percent of participants identified a racial category, but did not report an ethnicity. (Table 21)

Conclusion

NIH staff continue to monitor, document, and work with grantees and contractors to ensure compliance with the inclusion policy. Program officials provide technical assistance to investigators as they develop their applications and proposal throughout the application process. Review officials introduce and discuss with reviewers the guidelines and instructions for reviewing the inclusion of women and minorities in clinical research, as well as the instructions and requirements for designing Phase III clinical trials in which valid analyses can be conducted for sex/gender and ethnic/racial differences. At the time of award and submission of progress reports, program officials monitor and verify that inclusion policy requirements are met. When new and competing continuation applications that are selected for payment are deficient in meeting policy requirements, grants management staff and program officials will withhold funding until the principal investigator has satisfactorily addressed the policy requirements. Analysis of the FY 2003 and FY 2004 inclusion data show that substantial numbers of women, non-minority men, and minorities have been included as research subjects in intramural and extramural Phase III clinical trials and other human subject research studies. NIH continues to ensure that women, non-minority men, and minorities are included in NIH-funded human subject research.

ORWH Career Development Programs

ORWH addresses the career development of girls and women in biomedical careers across their life spans, from initial interest in science while in grade school to advancement through their careers. In addition, ORWH focuses its efforts on career development for both women and men in careers in women's health or sex/gender research. In collaboration with NIH institutes, centers, and offices, ORWH developed and implemented numerous educational outreach programs for girls in middle school and women in high school, college, graduate school, and postdoctoral programs. ORWH also implemented a special re-entry program for women who take time off from their careers to start a family or care for family members. In addition, ORWH developed the Achieving Excellence in Science (AXXS) program to engage scientific societies in advancing women in their established careers.

ORWH is mandated to develop opportunities for and to support the recruitment, retention, re-entry, and advancement of women in biomedical careers. The foundation for accomplishing these goals was laid in recommendations from public hearings and a career development workshop entitled *Women in Biomedical Careers: Dynamics of Change; Strategies for the 21st Century*. ORWH invited and interacted with the scientific and medical communities, organizations with an interest in women's health, Congress, and other components of government about NIH programs related to women's health. Over the years, ORWH developed and expanded career development programs commensurate with the budgetary increases for ORWH.

The career development workshop underscored that gender bias in the sciences impeded professional advancement for women long before entry into the workplace. The cultural and institutional barriers begin for many young women in the early years of their scientific training and are key determinants in their decisions about whether to pursue a career in science or choose another profession. Barriers to the success of women in biomedical careers and other related factors that were identified can be summarized as follows.

- Recruiting women and girls into scientific careers
- Lack of female role models and mentors
- Career paths/rewards (salaries, promotions, etc.)
- Family responsibilities/dual roles
- Need for re-entry into biomedical careers
- Sexual discrimination and sexual harassment
- Gender sensitivity
- Racial bias/special needs of minority women
- Research initiatives on women's health

The report from this effort, *Women in Biomedical Careers: Dynamics of Change; Strategies for the 21st Century*, continues to serve as the basis for ORWH activities to fulfill its mandate to foster women's participation and advancement in biomedical careers. ORWH has undertaken numerous activities to increase opportunities for women, including minority women, in biomedical careers, as well as to promote the interest and sustain the research participation of both women and men.

With expanding horizons in biotechnology and science, there is a need for greater participation by women in investigations that will open new frontiers of knowledge about health, disease, and scientific technology. While exact figures are not available for those who are pursuing careers in biomedical research, ORWH recognizes that there is a need to increase not only the numbers of women who are biomedical and behavioral investigators, but also the numbers of women who are in policymaking positions that can influence or determine the direction of research initiatives.

ORWH initiated a number of programs to nurture the participation and advancement of women in biomedical careers in order to ensure that interest and priorities in women's health remain at the forefront of our nation's research agenda. ORWH has developed strategies and programs to implement the recommendations made at this workshop and to address career issues, barriers, and concerns of women and minorities in science. These programs include support for mentored research training in areas related to women's health; support for biomedical scientists who have interrupted careers in research in order to fulfill family obligations to re-start their research careers; outreach to young girls and women who have an interest in pursuing careers in biomedical science; and collaboration with professional societies to encourage their support of the career advancement of women scientists.

Re-entry into Biomedical and Behavioral Careers

ORWH developed a pilot program to encourage fully trained women and men to re-enter research careers after taking time off to attend to family needs. The success of this pilot program led to the expansion of the program across NIH. The ORWH Re-entry Scientist Program is currently supported by several ICs and was reissued in FY 2004. ORWH conducted an assessment of re-entry scientists' success in obtaining grants from NIH and other institutions.

The ORWH Re-entry Program helps fully trained scientists (women and men) reestablish careers in biomedical or behavioral science after taking time off to care for children or parents, or to attend to other family responsibilities. The aim of these supplements is to encourage fully trained individuals to re-enter research careers within the missions of all the program areas of NIH. This program provides administrative supplements to existing NIH research grants for the purpose of supporting full- or part-time research by these individuals in a program geared to bring their existing research skills and knowledge up to date. It is anticipated that at the completion of the supplement, the scientist will be in a position to apply for a career development (K) award or for a research award. To date, more than 55 women and men have received re-entry supplements. Recent examples follow.

Title: *Examining the Efficacy of "Parents Who Care"*
PI: Kevin P. Haggerty, M.S.W.
University of Washington
Awardee: Elizabeth McKenzie, Ph.D.

In September 1998, the candidate had a baby and was interested in using the extra time to

develop a strategy for pursuing a mentored research career award. However, due to her husband's job loss, they opted to move to the Seattle area to live near extended family and gain support for child rearing, to live in a city with a larger job market and opportunities for her spouse, and to have a job with a flexible schedule to provide care for her young child. She worked at the Committee for Children for nearly 3 years and spent the first year working full time on a large clinical trial (Steps to Respect Evaluation Study), contributing substantively to the study design, recruitment of subjects, and to the development of a student self-report (Committee for Children Research Team, 2000).

This project, funded through August 31, 2005, is a 5-year experimental test of the efficacy of PWC (Parents Who Care), a theory-based drug abuse prevention intervention for families with early adolescents. The study, being conducted with African American and European American families in the greater Seattle area, has three conditions: 1) a family self-administered curriculum with telephone followup (SA); 2) a family self-administered curriculum plus parent and teen skills group (PAG); and 3) a no-treatment control condition. (5 R01 DA 12645-03)

Title: *Preventing Conduct Problems—Promoting Social Competence*
PI: Carolyn Webster-Stratton, Ph.D.
University of Washington
School of Nursing
Awardee: Jamie Nekich, Ph.D.

Dr. Nekich's research career has been on hold since 1997, when she was last employed in a full-time, tenure-track faculty position at California State University–Sonoma. In the summer of 1996, her son was diagnosed with Asperger's Disorder. The demands of her son's disorder had prompted her to resign from her first tenure-track position at the University of Southern California in 1995, to accept a position at California State University, which she believed would be less demanding and allow her to attend more effectively to her son's needs. However, after her first year at California State University, it became clear that the needs of her son were increasing and that maintaining any employment was no longer feasible. Their family made the decision to relocate to an area where they could live on her husband's income alone and she could become a full-time care giver to her son. Her husband accepted a full-time position at the University of Idaho. During the first year in Idaho, she also gave birth to a second child. In 1998, the demands of her youngest child and caregiving responsibilities for her older son decreased, allowing for some part-time employment.

The purpose of the project is to take empirically supported, clinic-based treatment programs for child oppositional and conduct disorders (ODD/CD) and evaluate their short- and long-term efficacy as school-based, early intervention programs for preventing ODD/CD, one of the most important behavioral predictors of substance abuse and delinquency. (5 R01 DA 12881-02)

Title: *The Role of Dab2 Tumor Suppressor*
PI: Jonathan Cooper, Ph.D.
Fred Hutchinson Cancer
Research Center
Awardee: Susan Veals-Onrust, Ph.D.

Dr. Onrust received her doctorate at New York University in 1992 and took an 8-year hiatus from research to raise three children in New Zealand. Her postdoctoral work was at the University of California–San Francisco, resulting in one publication. She returned to the United States and has worked as a nurse since 1992. Under the supplement, Dr. Onrust will investigate the role of Dab2 as a tumor suppressor. This project fits with her background in cell culture, and she has the biochemical skills needed to carry out the experiments. (GM 66257)

Women's Reproductive Health Research Career Development Centers

ORWH joined NICHD in the development of a Request for Applications (RFA) to invite institutional career award applications for Women's Reproductive Health Research

(WRHR) Career Development Centers. These centers support research career development of obstetrician-gynecologists, known as WRHR scholars, who recently completed postgraduate clinical training and were commencing basic, translational, and/or clinical research relevant to women's health.

The overall goal of the program is to bridge clinical training with research independence through a mentored research experience leading to an independent scientific career addressing women's reproductive health concerns. The emphasis is on research relevant to obstetrics and gynecology and/or its subspecialties: maternal–fetal medicine, gynecologic oncology, and reproductive endocrinology and infertility. Related fields, such as adolescent gynecology, urogynecology, and the reproductive health of women with disabilities, are also included. Mentors with established research programs covering a broad range of basic and applied biomedical and biobehavioral science related to obstetrics and gynecology, together with collaborating departments, form the intellectual and technical base for mentoring junior faculty accepted into the program.

Since inception in FY 1998, approximately 86 junior faculty members have entered the career development program. A new RFA (HD 030-020) was issued in FY 2003, with ORWH funding the following sites:

- *UCLA Women's Reproductive Health Research Center*
  Gautum Chaudhuri, M.D., Ph.D.

  The overall theme of this center is to emphasize a fundamental approach to the diseases of women that includes the disciplines of developmental biology, molecular genetics and cell biology, and behavioral science, as well as translational and clinical investigative research. The institutional commitment includes support for the initial preparatory training of scholars in research fundamentals. Scholars receive solid training by accomplished scientists who are well funded and have distinguished records of research and mentoring. In view of the multidisciplinary activities of the center, faculty mentors from other departments who are part of the mentor pool seem to better appreciate the problems related to women's reproductive health.
  (2 K12 HD001281-06)

- *The Yale WRHR Career Development Center*
  Charles J. Lockwood, M.D.

  This two-tiered approach to education and training that involves progressive steps toward individualizing a scholar's training in collaboration with the mentor and drawing from extensive departmental and institutional resources. Dr. Lockwood identified three research tracks: basic, translational, and clinical. A strong feature of the center is the initial practical training in basic laboratory techniques and methods in cellular and molecular biology. The department of obstetrics and gynecology has a successful record in training academic clinicians and scientists. Mentors are accomplished basic and clinical scientists with extensive experience in mentoring. There is a comprehensive plan for developing a WRHR center that is likely to succeed in creating a center of excellence for training and developing a new generation of independent investigators in the field of women's reproductive health.
  (1 K12 HD047018-01)

- *Women's Reproductive Health Research at the University of Washington*
  David A. Eschenbach, M.D.

  The overall goal of this center is to provide junior faculty trained in obstetrics and gynecology with the necessary training and research skills that will allow them to embrace a career in academic medicine related to women's reproductive health. Faculty identified as mentors are highly qualified and constitute a network of excellent to outstanding clinical and basic science research scientists that offers a wide variety of research opportunities. Candidate scholars identify a mentor and submit a research proposal prior to submitting an application.
  (2 K12 HD001264-06)

- *Women's Reproductive Health Research Career Development Center*
  Joanna M. Cain, M.D.

  The goal of this center is to provide a stimulating and nurturing environment for junior faculty with competitive credentials and a strong interest in research. Faculty mentors are an interactive and cohesive group of established scientists who represent comprehensive and complementary interests and expertise within the fields of reproductive health. The center encompasses preclinical research on models ranging from lower systems to nonhuman primates with cutting edge clinical investigations in women's reproductive health research. A unique aspect of the research plan is targeted to increase the competency of clinical investigators. Another attractive element is the broad application and adaptability that can be individually tailored to the scholar. (2 K12 HD001243-06)

- *UTMB WRHR Career Development Center of Excellence*
  Garland D. Anderson, M.D.

  This excellent program targets a broad-based, basic research approach to women's reproductive health problems. The center focuses on training in molecular biology, cell biology and physiology, and clinical sciences. Mentors have strong research credentials with a very solid record of accomplishments in training academic faculty in women's reproductive health research. A strength of this center is the commitment to diversity, as demonstrated by their successful recruitment of underrepresented minorities. (2 K12 HD001269-06)

- *Women's Reproductive Health Research (UCSF)*
  A. Eugene Washington, M.D.

  The principal mission of this center is to promote health and prevent disease by expanding the pool of well-trained, productive investigators in women's reproductive health research. The structured program is of sufficient duration, relevant didactic education, and immersion into a vibrant, intellectually challenging, research community leading to academic independence. Scholars are recruited to pursue biomedical research and clinical research. (2 K12 HD001262-06)

- *Mentoring and Advanced Research Training for WRHR Scholars* (Stanford)
  Mary L. Polan, M.D., Ph.D.

  This center capitalizes on career development and advanced training in basic and clinical research in women's reproductive health. Scholars are exposed to structured research and didactic experiences having the scope and rigor of an advanced research degree with mentoring by highly trained and experienced faculty with proven records of excellence in research and career development. Each trainee has two mentors: a primary mentor for research and a secondary mentor for clinical continuity. Scholars are mentored in reproductive biology and endocrinology, a major strength at the institution, and clinical and epidemiologic research. (2 K12 HD001249-06)

- *Center for Career Development in Women's Health* (Penn State)
  Michael T. Mennuti, M.D.

  The goal of this center is focused on cultivating a cadre of independent scholars in women's health, emphasizing multidisciplinary approaches. The center identifies talented physicians who have demonstrated potential for successful careers in research, places them in an exciting and supportive research environment under the guidance of an experienced mentor, and advances their skill sets in research to the point that they can establish a productive, independent line of investigation. The program is tailored individually to each scholar's interest and talents. (2 K12 HD001265-06)

- *Detroit Reproductive Career Development Research Center* (Wayne State)
  John M. Malone, M.D.

  This center provides each scholar with a mentored research experience relevant to his/her long-term research interest. The center proactively networks each scholar with senior, well-established investigators prominent in the scholar's field of research.

The cadre of experienced, extramurally funded mentors to train scholars provides a firm basic and clinical research base that spans the broad spectrum of contemporary research that is relevant to women's health. (2 K12 HD001254-06)

- *Women's Reproductive Health Research Scholars Program* (University of Colorado) Baha M. Sibai, M.D.

  This center focuses on enhancing the research skills and expertise in academic obstetrics and gynecology. The primary emphasis of the program is to enhance the basic research skills and expertise of the scholars and familiarize them with modern scientific techniques and principles, which they can subsequently apply to clinical problems in obstetrics and gynecology. The program provides scholars with extensive training in basic research methods, coupled to a tight, mentor-guided research project and strong graduate-level coursework. (2 K12 HD001256-06)

Sackler Faculty of Medicine/ Tel Aviv University Students

In conjunction with the NIH Office of Intramural Research, a Bi-national Student Exchange Program in Women's Health Studies was initiated in FY 2001 with the Sackler Faculty of Medicine at Tel Aviv University (TAU), Tel Aviv, Israel. This program exposes five excellent M.D.-Ph.D. or Ph.D. Israeli students in the biomedical field each year to the leading research programs at NIH. The program encourages those interested in research related to women's health, whether basic, patient-oriented, or population-based. The program facilitates and enhances biomedical research in Israel, establishes scientific collaborations between Israel and NIH, and trains promising students for postdoctoral studies at NIH. This program offers an opportunity to present new horizons for research into women's health issues and provides a pioneering model for other medical faculties and other countries.

A joint TAU–NIH chooses the best students to join the program each year, with a maximum of ten at any given time. These students have an Israeli advisor and an American advisor. The students perform research 10 months a year in the Israeli laboratory and up to 2 months a year in the NIH laboratory, for a total of 4 to 5 years of research. Once a year, the American supervisors visit Israel for a joint scientific meeting of all enrolled in the program. The program favors excellence, students enrolled in the M.D./Ph.D. program, women, and minorities.

Achieving Excellence in Science

ORWH, in conjunction with the American Society for Cell Biology and NIEHS, convened Achieving Excellence in Science (AXXS) '99 to explore the roles of scientific societies in advancing science by building the careers of all women in science, from the predoctoral stage to the senior scientist level. The workshop was held in FY 1999 as a satellite meeting to the American Society for Cell Biology's Annual Meeting in Washington, DC. More than 140 participants, representing over 50 scientific societies, organizations, and government agencies, gathered to:

- develop action items that societies could consider for their membership,
- contribute to an annotated bibliography of the career resources that could be made available as a national resource on the Internet, and
- exchange information with other workshop participants on the strengths and weaknesses of existing and planned societal programs and resources for their women members.

The full report on AXXS '99 is available online at *www4.od.nih.gov/axxs/*. As follow up to the AXXS meeting, ORWH developed, designed, launched, and now maintains an AXXS web page, which will serve as a primary resource for women in biomedical sciences (*www4.od.nih.gov/axxs/*).

In FY 2002, the Committee on Women in Science and Engineering (CWSE) of the National Academy of Sciences held a workshop to gather representatives of clinical societies and discuss ways for the societies to enhance the participation of women scientists in the clinical research workforce. Focus was placed on identifying initiatives and action items that clinical societies can adopt, ways for clinical societies to disseminate successful strategies, and ways to collaborate among societies. The workshop focused on:

- initiatives and action items clinical societies can adopt within their organizations to enhance women's advancement in the clinical research field;
- ways for clinical societies to disseminate successful strategies to advance women's careers; and
- ways that clinical societies can collaborate to promote women's contributions to their fields.

A report from this meeting, Achieving XXcellence in Science: Role of Professional Societies in Advancing Women in Science: Proceedings of a Workshop, AXXS 2002, is available from the National Academies at *http://books.nap.edu/catalog/10964.html*.

The AXXS Coordinating Team (ACTeam) encourages and assists scientific societies and other professional organizations to implement and sustain initiatives to advance the careers of women in science. The AXXS 2002 recommendations stated that career development for women needs to provide training programs that include financial, academic, scholarship, grant writing, conflict management, negotiation skills, and full career development workshops.

In FY 2004, ORWH supported a new endeavor of small partnership meetings. For example, the Society for Neuroscience in San Diego collaborated with the Society for Neuroscience to sponsor a partnership meeting, held under the auspices of the Professional Development Workshop series. It is one of several initiatives ORWH is co-sponsoring with professional societies to address the needs of their members, as well as to enhance their scientific missions in the United States and internationally. Based on the outcome of this meeting, several other such partnership meetings are being planned.

Accomplishments

The Core ACTeam plans to conduct partnership meetings in conjunction with the Society for Neuroscience and the American Society for Cell Biology in FY 2005. These interactive meetings will present a history of AXXS, current statistics related to women in science, and discussions about the role of the society in the advancement of the careers of women. These partnership meetings are a vehicle to partner with a society both to help the society assess its current programs to assist the careers of women and to share knowledge/information/initiatives that are part of the AXXS network.

The Core ACTeam also is developing a tool for societies to assess themselves in terms of: participation of women scientists in society activities, climate for women in the society, and current or potential "value added" benefits for women members.

In addition, the ORWH AXXS website is currently being upgraded to expand from its original scope of a report on AXXS '99 to include current AXXS-related information and "Effective Practices" that scientific societies have submitted to describe their initiatives to advance the careers of women in science. The "Sixteen Effective Practices" have been updated and are being printed for partnership meetings and posted on the AXXS website.

Intramural Program on Research on Women's Health

The ORWH/NIH Intramural Program on Research on Women's Health's (IPRWH) successfully established an innovative interdisciplinary program in women's health research in the Intramural Research Programs (IRP). A steering committee was formed to develop, implement, and bring this program to fruition. (Appendix I) The IPRWH was created to serve as the focal point for all

women's health research, including sex and gender comparisons, within the IRP. The mission of the IPRWH is to: 1) promote, stimulate, and support efforts to improve the health of women through biomedical and behavioral research within the IRP; 2) enhance communication among, and recruitment of, researchers on women's health among the institutes and centers; and 3) enhance interdisciplinary research through the development of specific training programs and recruitment of new clinical and basic research trainees into the IPRWH.

Achievement of these goals is well underway. The Women's Health Special Interest Group (WHSIG) is a highly successful and well-attended scientific lecture series established to serve as a forum for researchers across NIH to share research ideas and methodology, develop collaborations, and learn about sex-based differences beyond the effects of hormones that are relevant to molecular, cellular, genetic, and developmental processes and that affect organ systems, behavior, and the organism as a whole. WHSIG lectures have been held monthly since November 2002 and have been presented by experts in women's health research from within the NIH intramural program as well as the outside scientific community. (Appendix J) This lecture series has provided an important forum for scientific interchange and establishment of collaborations between NIH IRP researchers with scientists around the world, highlighting an interdisciplinary approach to sex and gender differences in biology and disease from the molecular level to therapeutic clinical trials.

Four intramural training programs in women's health have been developed: Clinical Fellowship in Women's Health, Shared Postdoctoral Fellow Program, Research Career Re-Direction Program, and Research Re-entry Program. These training programs will enable excellent inter- and multidisciplinary research in the area of sex/gender factors that influence the expression of health and disease.

ORWH also provides essential support to the Office of Education for the design and implementation of programs that foster the professional development of NIH trainees, in particular the postdoctoral fellows in both clinical and basic research programs across all institutes and centers. During FY 2003, ORWH supported programs to enhance the training experiences of participants in the NIH Postbaccalaureate Intramural Research Training (IRTA) program.

Report on the Status of Intramural Women Scientists Survey Update

ORWH supported the updated survey of the Second Task Force Study to look at the composition of tenure-track and tenured senior investigators and to determine, the need for mentoring and support networks. In addition, this study will update the areas covered in the first study conducted in the early 1990s. Topics to be addressed are: communication, visibility pay equity, tenure-track plan, and tenure. The task force will seek to identify impediments to the recruitment of women into tenure-track investigator positions and tenured senior investigator positions at NIH, and look at impediments to the retention and tenuring of female tenure-track investigators. In addition, it will look at career tracks/appointment mechanisms chosen by men versus women and the underlying reasons for the choices, and the recommendation of administrative and structural changes to correct identified problems.

***WISH-NET* Website**

ORWH, in collaboration with Public Responsibility in Medicine and Research (PRIM&R), a non-profit organization based in Boston that works to improve the diversity of both persons and opinions in science and medicine, established the Women In Science and Healthcare Network (WISH-net) website (*http://wish-net.od.nih.gov*). This website is continually updated to supplement effective and readily available, newly developed resources associated with mentoring, inspiring, and encouraging girls and women as they consider, embark upon, or struggle with careers in healthcare, science, or medicine.

WISH-net strives to provide resources for such a community, opportunities for finding mentors and roles models, and other support and encouragement for girls and women who may otherwise be discouraged from pursuing a career in the sciences. PRIM&R continues to build on its achievements by focusing on three separate dimensions:

- Review proposed new content;
- Add additional interactivity and networking opportunities; and
- Increase awareness of the site through outreach and marketing.

WISH-net is divided into sections for middle/high school, college/graduate students, and professional women, representing the changing needs of girls and women as they advance and develop into different stages of their lives and careers. Each section promotes education, resources, professional and personal development, inspiration, and mentoring.

In developing the WISH-net website, PRIM&R also conducted usability and attractiveness focus groups with seventh graders. The girls were very candid in their responses and suggested, among other things, more color and interactivity on the site. The focus group also commented that the WISH-net website should not "talk down to them," but rather encourage the girls to pursue engaging and interactive science activities. These focus groups led to the development of a website that was attractive to a middle school audience as well as to more mature audiences. The current site allows access to the material appropriate for each age group through a user-friendly portal.

Association for Women in Science Seminar Series

The Association for Women in Science (AWIS) Bethesda Chapter addresses issues and concerns of women in science. ORWH provided support for the annual AWIS Bethesda Chapter Seminar Series, Strategies for Success in Science. Seminars included: From the Bench to Bioethics, Tools vs. Therapeutics: Opportunities for the Entrepreneur, Career Opportunities in the Sciences: The Times Are A'changin. . ., Networking 'Know How' for Women in Science, Networking Opportunities Workshop, and My Journey as a Student of Science.

In addition to these programs, ORWH supports ongoing projects and has initiated specific training projects that include opportunities for high school students, college faculty and students, and minority students to obtain research experience or exposure to current scientific concepts through NIH. ORWH also developed and supported a number of programs for the advancement of girls and women in science through collaboration with the NIH Office of Science Education, including a video series featuring minority women surgeons, researchers, and pathologists and an online curriculum designed to spark interest in biomedical sciences among middle school and high school students.

ORWH–FAES–NIH High School Student Summer Program

The summer program hosted 24 new high school students and 17 returning students. There were 26 women and 15 men, including 11 minorities (two African American women, one Hispanic woman, and one Hispanic man). Students came from both public and private schools in Maryland, Virginia, and the District of Columbia to to gain exposure to science at NIH in intramural labs.

Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds

The Office of Loan Repayment and Scholarship, OIR, is responsible for the development and management of the Undergraduate Scholarship Program for Individuals from Disadvantaged Backgrounds. This program provides scholarships to undergraduate students who have been competitively selected from a nationwide pool of candidates. An

average of 15 scholarships are awarded each year.

Loan Repayment Program for Health Disparities Research

The objective of the Health Disparities Research Program is to recruit and retain highly qualified health professionals to research careers that focus on minority health or other health disparities issues. The program provides for the repayment of educational loan debt of qualified health professionals who agree to conduct minority health or health disparities research for two years. The program provides for the repayment of the principal and interest of the educational loans, up to $35,000 per year.

ORWH/Office of Education Joint Programs

ORWH provides essential support to the Office of Education for the design and implementation of programs that foster the professional development of NIH trainees, in particular the postdoctoral fellows in both clinical and basic research programs across all institutes and centers. During FY 2003, ORWH supported programs were again implemented to enhance the training experiences of participants in the NIH Postbaccalaureate Intramural Research Training (IRTA) program.

Programs for Postdoctoral Trainees

In 2003, OE planned and implemented a broad-based educational program designed to provide NIH postdoctoral fellows with the requisite skills necessary to compete for and sustain careers in biomedical research and science-related occupations. Survival skill workshops included:

Survival Skills Workshops

- *CV/Resume Writing* – This included a workshop that focused on the development of resumes and CVs that maximize an individual's training and experience.
- *Grant Workshop* – This workshop covered the preparation and submission of research grant proposals, as well as the review and funding process. Participants were provided with a wealth of information and strategies that will be invaluable to fellows as they seek funding support to begin their academic careers.
- *Negotiating* – Participants learned the skills that are necessary when negotiating a job offer.
- *Job-Hunting* – This workshop covered when and how to seek career opportunities; what employers look for; researching positions; writing effective cover letters, CVs, resumes, statements of interest, and letters of recommendation.

Science Communication Courses

- *Writing about Science* – This class, taught by the editor of the *Journal of the National Cancer Institute*, taught fellows how to write articles suitable for publication in peer-reviewed scientific journals. Participants learned how to write a research paper using their own laboratory data. During the course, they critiqued the work of others and learned about responsible authorship; the process of publication; dealing with editors and reviewers; and other issues related to scientific writing.
- *Speaking about Science* – This course provided participants with information on how to become an exemplary speaker, to excel in job interviews, and how to deliver scientific presentations using visual aids, including video feedback.
- *Advanced Speaking about Science* – This course was assisted fellows in building upon the lessons of the introductory course, provided vocal and other technical instruction, discussed new methods of presentation, and offered a forum for in-depth assistance on the individual needs of the participant.

Career Workshops

The OE also sponsored three workshops that focused on careers that would enable fellows to utilize their biomedical research training:

- *Careers in Patent Administration* – This workshop focused on career opportunities in patent administration for individuals with scientific training.
- *Teaching at a Small College and a Large University* – This workshop compared the differences between academic life at small colleges and large research universities.
- *Careers in Bio-Defense* – This workshop focused on emerging scientific career opportunities in bio-defense.

Job Fair for Postdoctoral and Clinical Fellows

The Job Fair featured 28 exhibitors from academe, biotechnology firms, and government. This year's program, coordinated by the Office of Education with some assistance from the Fellows Committee, also included a keynote address by Dr. Edward Scolnick, President Emeritus, Merck Research Laboratories, who discussed "Therapeutic Advances Through Genomics: Opportunities and Limitations." The evaluation ratings by exhibitors were the highest ever.

Programs for Postbaccalaureate Trainees

- *Interviewing* – This workshop provided postbaccalaureate trainees with information on how to prepare for medical school interviews. It included a focus on the interviewing process from the representative of the admission committee's point of view, including suggestions for preparing for a successful interview.
- *How to Give a Scientific Presentation* – This two-part workshop focused on developing a scientific presentation, and how to deliver a scientific talk.
- *Test-Taking Skills* – These classes focused on preparing for the Graduate Record Examination (GRE) and the Medical College Admission Test (MCAT). Divided into three sessions for the GRE and three sessions for the MCAT, the course included an insight into the application process, types of questions, the need for review courses, and the development of a preparation strategy and schedule.
- *Tips on Preparing Your Poster* – This two-part workshop focused on preparing a scientific poster, and the evaluation of individual poster.
- *Postbacalaureate Poster Day* – The third annual Postbaccalaureate Poster Day was held on May 7, 2003. This event provided an opportunity for postbaccalaureate trainees to share their research with the NIH community. The participants represented virtually all Institutes and Centers with intramural programs.
- *Premed Advising Workshop* – The purpose of this workshop was to provide information regarding the admissions process to postbaccalaureate trainees who are interested in applying to medical school or to combined M.D./Ph.D. programs.
- *NIH Academy Curriculum* – The NIH Academy, a postbaccalaureate program for recent college graduates with an interest in pursuing careers that focus on the elimination of domestic health disparities, enrolled its fourth class during the academic year 2002-2003. ORWH support covered honoraria for three speakers who discussed a range of topics including oral presentations, interviewing techniques, public health programs, and the IOM report on health care and minorities.

Fellows Award for Research Excellence (FARE)

The tenth annual NIH-wide FARE competition (FARE 2004) provided recognition for the outstanding scientific research performed by intramural postdoctoral fellows. The award is sponsored by the NIH Fellows Committee, the Scientific Directors, the Office of Research on Women's Health, and the NIH Office of

Education, and is funded by the IC scientific directors and ORWH. Fellows submit an abstract of their research, which is peer reviewed in a blind study section competition. Winners of FARE awards each receive a $1,000 stipend to attend a scientific meeting at which they present their abstracts, either as a poster or a seminar. In FY 2003, there were 203 winners with ORWH providing funds for 51.

PUBLIC INFORMATION AND OUTREACH/EDUCATION

ORWH works in partnership with NIH institutes and centers, other federal agencies, and various national, state, and community organizations utilizing various outreach efforts to disseminate information on research on women's health. Working together, the partners ensure timely and relevant information is distributed to advocacy groups, public and private institutions at all levels, and to concerned individuals interested in women's health research. Outreach through ORWH advocates is a central method to disseminate the latest information and research on women's health. ORWH also provides science-based information on women's health research to the public, health professionals, voluntary organizations, and other key stakeholders. The goal is to encourage women to seek and use information on research on women's health and to serve as a central resource at NIH on women's health research. ORWH strives to reach all socioeconomic groups of women, including underserved populations such as racial or ethnic minority groups, women of all ages, and women living in both urban and rural areas.

Among the many activities and responsibilities of ORWH, outreach to minority communities continues to be an area of focus. Utilizing a multi-pronged approach, the office provides information, guidance, and direction to minority groups and organizations, assisting these communities in addressing health care needs for women.

ORWH collaborates with many health advocacy community minority health organizations to disseminate information on specific health issues addressing women in their communities, the importance of including minority women as subjects in clinical research, and current information generated from research funded by NIH. Several recently updated publications, *Women of Color Health Data Book* and the *Outreach Notebook*, are widely distributed resources to the public. These documents contain information about several minority women's health issues, including cancer, diabetes, obesity, and cardiovascular and infectious diseases. These and other ORWH and NIH documents inform the public of NIH's efforts to reach out to the minority community and communicate techniques for recruiting and retaining minorities and women in clinical research. ORWH also participates as an exhibitor or by providing women's health information to many conferences, professional organizations, community workshops, religious group activities, and gatherings with an interest in women's health.

ORWH participates on several organizational and interagency committees, in conference planning, and information dissemination on current research funded by NIH. In 2004, ORWH distributed materials to organizations throughout the country, such as the Morgan State University, the National Medical Association, the Asian American Psychological Association meeting, the League of United Latin American Citizens, the National Black Women's Health Network, and Hadassah, about research addressing health issues of their communities. In addition to presenting many speeches on women's health research to various groups, ORWH meets with numerous representatives of the scientific and advocacy communities. ORWH provides materials and guidance through various groups, such as the National Osteoporosis Foundation, Indian Powwow Common Ground Powwow, greater Southeast Community Hospital, Morgan State University, Delta Sigma Theta Sorority, and Village Baptist Church of Maryland.

ORWH has also worked with various federal and international agencies to help promote health awareness and minority women's representation in clinical research. The office participated in the planning and supported the DHHS/OWH Minority Women's

Health Summit held in August 2004 in Washington, DC, the Blacks in Government Forum on Health, and a departmental-wide symposium hosted by the Federally Employed Women. Internationally, ORWH held a meeting with the Korean Ministry of Health & Welfare, worked closely with the Fogarty International Center (FIC) on issues related to participation of women in clinical research, and held discussions on developing policy with the Canadian Ministry of Health.

ORWH Website

ORWH centers its outreach efforts to the scientific and public communities through its extensive website content—*http://orwh.od.nih.gov*. Continuously updated with the latest conference, upcoming seminars, and publication reports, the ORWH website averages more than 400 visits per day. ORWH is committed to providing valuable health information to the worldwide community; close to 20 percent of the website visitors are international. Among the key features of the ORWH website is the ability to download the latest publications developed by ORWH. The website mirrors the objectives of ORWH by tailoring the content to meet the needs of its diverse stakeholders. For example, for the research community, there is a section dedicated to women in biomedical societies through the AXXS program. In ORWH's attempt to reach out to middle school girls who are considering careers in science and research, a website to foster career interest and mentors was designed through the development of the women in science health care network (WISHnet). The site contains information on policies, programs, and activities related to women's health sponsored by NIH and by other federal agencies. The site also contains an annotated list of online resources for information on diseases that affect the health of women, as well as links of interest to women in biomedical careers. Copies of NIH and ORWH publications may be downloaded and/or ordered from the website, including English and Spanish versions of an ORWH-supported publication, *Women of Color Health Data Book*.

ORWH firmly believes in a mosaic, interdisciplinary model on women's health. Visitors are able to retrieve summary reports from all relevant NIH institutes on their research in women's health and key research findings across academic research communities from ORWH-supported programs, such as Building Interdisciplinary Research Careers in Women's Health (BIRCWH) and Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR). Key areas of research, which are highlighted on the ORWH website, include chronic fatigue syndrome, uterine fibroids, and menopausal hormone therapy. The Menopausal Management and Hormone Therapy section of the website includes valuable links to multiple studies, conferences, and news on menopausal hormone therapy throughout NIH. ORWH is committed to ensuring inclusion of women into clinical studies and provides the most recent reports in its inclusion of women in research section. ORWH continuously strives to be a resource for the scientific and public communities. Future additions to the ORWH website will include tools for researchers and multimedia presentations.

ORWH Women's Health Seminar Series

Since 1991, ORWH has supported a women's health seminar series to provide the state of the science on issues of importance to NIH and outside communities. This seminar series features nationally recognized leaders in women's health research who present the latest information on topics important to women's health. Seminars are free and open to the public. Topics are selected by a trans-NIH seminar series committee based on relevant, timely, and pertinent topics in women's health. Seminars in FY 2003 included: Respiratory Health and Diseases in Women; Cancers in Women: New Approaches; Alcohol: A Women's Health Issue; and Boning Up on Osteoporosis: Emerging Therapies for Prevention and Treatment. In FY 2004, ORWH seminars addressed Women and Heart Disease, Alternative Medicine and Women's Health, and Women and Obesity. (Appendix K)

ORWH/Office of Science Education Joint Programs

ORWH and the Office of Science Education (OSE) have worked together to provide educational resources for pre-college students and others who are interested in science and health. ORWH supports a Women are Scientists video and poster series that provides colorful, informative videos and posters for middle school students that feature women scientists. The series is designed to stimulate the interest of girls in science at a time when they are making decisions about the course choices that may affect their career options later. In the middle school years, many girls are discouraged from pursuing advanced levels of study in math and science. This series is intended to make them aware of the many interesting and rewarding careers in the medical sciences and the educational requirements necessary to pursue them. Areas include: Women are Surgeons, Women are Pathologists, and Women are Researchers. The fourth video kit, Women Scientists with Disabilities, is in development. The kits are being used by teachers in the classroom, as well as by professional organizations, vocational centers, and by institutions, such as the Princeton Environmental Institute, for conferences targeting girls in science. The NIH National Library of Medicine has used clips of eight out of the nine women scientists that were profiled in the first three videos. These clips are a part of their new exhibit, Changing the Face of Medicine: Celebrating America's Women Physicians.

Speakers Bureau

A speakers bureau was developed by ORWH and is now housed at the OSE. It is a program designed to increase national visibility of NIH through employees who are available to speak at schools and other organizations about NIH research. Speakers are from a variety of occupations, including administrators, health care workers, librarians, and historians, as well as research scientists and clinicians. They address a total of 49 topics, such as osteoporosis, depression, and breast and ovarian cancers, with 340 subtopics. The speakers are diverse in their fields of expertise and their gender, race, and ethnic backgrounds.

Budget

SUMMARY OF NIH BUDGETARY EXPENDITURES ON WOMEN'S HEALTH, MEN'S HEALTH, AND RESEARCH APPLICABLE TO BOTH, FY 2003 AND 2004

The amounts of funding NIH invested in research during FY 2003 and FY 2004 specific to women, men, or applicable to both are presented in this budget summary. The budgetary figures presented in this report were provided and submitted by the budget officials at the individual NIH institutes and centers, then compiled by the NIH Office of Budget and submitted to the Office of Research on Women's Health for inclusion in this report.

"Women's health conditions," as defined in section 486 (f) of the NIH Revitalization Act of 1993, include all diseases, disorders, and conditions that are —

(A) unique to, more serious, or more prevalent in women;

(B) for which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women; or

(C) with respect to which there has been insufficient clinical research involving women subjects or insufficient clinical data on women.

Research on women's health conditions includes research on preventing such condtions and applies to women of all ages, and ethnic and racial groups.

ORWH has collaborated with the U.S. Department of Health and Human Services (DHHS) Coordinating Committee on Women's Health—composed of the Office of Women's Health on the Office of the Secretary, as well as the DHHS Office of Budget, Technology and Finance and other women's health offices and programs across DHHS agencies—to coordinate and standardize the procedures for reporting budgetary expenditures on women's health throughout the DHHS. This procedure ensures uniformity and consistency in reporting figures on women's health, and will formalize the data collection role of the budget office of the respective agencies.

The approach to data collection for this report is similar to that employed for reports since 1993-94; however, recent changes in the methodology for calculating disease spending changed, thereby reflecting a decrease in some women's health spending categories. Changes in methodology include the elimination of multiplying the expenditure by prevalence percentage for diseases, disorders, or conditions when enrollment data are not available. Also, new disease areas were added to streamline disease reporting.

In earlier reports, the budgetary reporting on women's health expenditures focused on single-gender studies; studies to evaluate sex/gender differences; and studies of diseases, disorders, and conditions that are unique to women. Previous reporting also used prevalence data as part of the reporting criteria, and included research on diseases, disorders, and conditions that are not unique to one sex, but for which there is documented evidence of greater prevalence in one sex by a ratio of at least 2:1, or for which a specific gender-related consideration exists.

For the purposes of this report, budgetary expenditures are categorized as inseparably combined or supporting research on either women's health or men's health. As a step toward establishing a uniform procedure for determining the appropriate categorical allocations, ORWH requested the institutes and centers apply the criteria below, based upon discussions of the DHHS Coordinating Committee on Women's Health and the NIH Coordinating Committee on Research on Women's Health:

(1) For research on diseases, disorders, or conditions that occur primarily in women (such as breast cancer and osteoporosis), the entire amount for programs in these areas should be entered under the column listed "women." This includes clinical, applied, and basic research.

(2) For research on diseases, disorders, or conditions that occur primarily in men (such as prostate cancer and amyotrophic lateral sclerosis), the entire amount for programs in these areas should be entered under the column listed "men." This includes clinical, applied, and basic research.

Table 28

*DHHS–National Institutes of Health Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives** *(Dollars in thousands)*

	FY 2003 Actual				FY 2004 Actual			
	Women	*Men*	*Both*	*Total*	*Women*	*Men*	*Both*	*Total*
Cancer								
Breast cancer (Including mammography and other service)	$655,704	$0	$479	$656,183	$672,305	$0	$714	$673,019
Reproductive cancers:								
cervical	82,520	0	0	82,520	85,285	0	0	85,285
ovarian	115,317	0	186	115,503	108,862	0	186	109,048
vaginal, uterine, and other	43,180	0	0	43,180	40,772	0	0	40,772
Lung cancer	5,561	0	285,121	290,682	0	0	292,937	292,937
Colorectal cancer	6,326	0	272,164	278,490	0	0	280,421	280,421
Other neoplasms	162,368	53,435	3,195,344	3,411,147	117,039	62,251	3,333,883	3,513,173
Subtotal	**1,070,976**	**53,435**	**3,753,294**	**4,877,705**	**1,024,264**	**62,251**	**3,908,141**	**4,994,656**
Cardiovascular/Pulmonary								
Blood diseases	44,202	53,391	507,519	605,112	35,528	50,013	509,615	595,156
Heart disease	90,272	77,093	639,564	806,929	98,735	85,012	673,457	857,204
Stroke	55,235	54,909	160,629	270,773	52,431	52,809	150,029	255,269
Other cardiovascular diseases and disorders	109,524	84,301	593,834	787,659	121,489	96,152	644,873	862,514
Pulmonary diseases	64,348	67,642	444,738	576,728	51,851	53,703	457,620	563,174
Asthma	37,369	28,186	177,206	242,761	38,580	29,672	196,990	265,242
Other	8,837	8,022	186,264	203,123	8,101	7,659	205,506	221,266
Subtotal	**409,787**	**373,544**	**2,709,754**	**3,493,085**	**406,715**	**375,020**	**2,838,090**	**3,619,825**
Reproductive and Maternal/Child/Adolescent Health								
Contraception	29,624	2,935	1,250	33,809	34,860	6,815	0	41,675
Infertility	7,278	5,207	5,473	17,958	7,960	3,687	6,667	18,314
Female reproductive physiology	147,523	0	0	147,523	150,015	0	0	150,015
Hysterectomy	749	0	0	749	767	0	0	767
Endometriosis and leiomyomas (fibroids)	9,712	0	0	9,712	7,617	0	0	7,617
Pregnancy, pregnancy prevention, and maternal health	179,630	1,076	4,159	184,865	189,314	849	1,710	191,873
Diseases related to DES exposure	5,416	0	0	5,416	5,697	0	0	5,697
Female genital cutting	0	0	0	0	0	0	0	0
Other	4,211	60,866	587,354	652,431	4,321	49,799	607,482	661,602
Subtotal	**384,143**	**70,084**	**598,236**	**1,052,463**	**400,551**	**61,150**	**615,859**	**1,077,560**

Aging								
Menopause	45,579	155	0	45,734	42,423	146	1,944	44,513
Menapausal hormone and non-hormone therapy	13,109	1,595	0	14,704	14,737	1,832	0	16,569
Alzheimer's disease	35,410	5,589	545,006	586,005	27,782	5,489	533,502	566,773
Malnutrition in the elderly	0	0	0	0	451	0	2,208	2,659
Osteoarthritis	24,497	0	37,099	61,596	21,189	0	42,843	64,032
Osteoporosis	135,350	8,243	4,726	148,319	142,720	2,600	15,899	161,219
Women's Health Initiative	66,493	0	0	66,493	62,312	0	0	62,312
Other	44,531	7,525	408,160	460,216	55,673	7,195	394,745	457,613
Subtotal	**364,969**	**23,107**	**994,991**	**1,383,067**	**367,287**	**17,262**	**991,141**	**1,375,690**
Metabolism/Endocrinology								
Diabetes	$112,222	$158,195	$115,714	$386,131	$110,575	$155,817	$118,571	$384,963
Obesity	127,009	67,826	41,162	235,997	145,153	77,281	48,672	271,106
Hepatobiliary diseases	1,670	30	162,612	164,312	1,720	30	154,604	156,354
Thyroid diseases and conditions	0	0	1,026	1,026	0	0	1,198	1,198
Other	3,350	3,118	68,007	74,475	3,746	3,451	330,642	337,839
Subtotal	**244,251**	**229,169**	**388,521**	**861,941**	**261,194**	**236,579**	**653,687**	**1,151,460**
Substance Abuse								
Etiology (unspecified)	1,831	1,368	33,725	36,924	1,775	1,100	36,260	39,135
Epidemiology (unspecified)	1,475	1,302	18,723	21,500	1,423	333	18,774	20,530
Prevention (unspecified)	1,496	291	29,318	31,105	1,634	810	25,474	27,918
Treatment (unspecified)	2,780	0	38,666	41,446	1,853	2,018	36,078	39,949
Alcohol	1,375	283	201,991	203,649	925	597	210,789	212,311
Illegal drugs	163,941	307,186	499,801	970,928	168,670	407,814	418,447	994,931
Prescription drugs	0	0	4	4	0	0	0	0
Tobacco products	76	0	21,699	21,775	166	0	24,358	24,524
Other substances	0	0	495	495	175	0	1,752	1,927
Co-occurring substance abuse and mental disorders	99	74	5,527	5,700	494	0	5,417	5,911
Subtotal	**173,073**	**310,504**	**849,949**	**1,333,526**	**177,115**	**412,672**	**777,349**	**1,367,136**
Behavioral Studies/Programs								
Violence (Includes domesestic, abused women, and spousal abuse)	7,056	3,433	17,651	28,140	7,463	2,167	29,494	39,124
Tobacco use cessation	284	0	811	1,095	0	0	950	950
Physical activity and nutrition (promoting healthy behavior)	153	0	51,021	51,174	438	20	78,187	78,645
Other behavior change and risk modification	3,518	1,678	189,793	194,989	3,774	2,132	188,049	193,955
Caregiving	863	0	12,842	13,705	1,764	1	3,011	4,776
Other	16,114	2,000	297,627	315,741	3,763	1	329,254	333,018
Subtotal	**27,988**	**7,111**	**569,745**	**604,844**	**17,202**	**4,321**	**628,945**	**650,468**

Mental Health								
Etiology (unspecified)	0	0	7,414	7,414	0	0	7,803	7,803
Epidemiology (unspecified)	250	0	109	359	39	0	119	158
Prevention (unspecified)	0	0	134	134	0	0	1,247	1,247
Treatment (unspecified)	0	12	127	139	0	0	2,158	2,158
Depression and mood disorders	22,910	1,441	148,720	173,071	17,898	2,250	151,482	171,630
Suicide	0	361	13,062	13,423	0	311	13,356	13,667
Schizophrenia	541	253	112,044	112,838	430	176	137,654	138,260
Anxiety disorders	2,847	3,813	24,774	31,434	2,731	3,336	36,626	42,693
Eating disorders	6,880	118	4,237	11,235	6,668	198	4,872	11,738
Psychosocial stress	6,985	516	32,604	40,105	6,606	27	30,383	37,016
Post-traumatic stress disorder (PTSD)	2,890	1,113	13,646	17,649	4,238	1,369	14,448	20,055
Other mental disorders (excluding Alzheimers)	2,483	3,013	642,349	647,845	16,624	4,941	638,825	660,390
Subtotal	**45,786**	**10,640**	**999,220**	**1,055,646**	**55,234**	**12,608**	**1,038,973**	**1,106,815**
Infectious Diseases								
AIDS/HIV	258,883	105,081	1,866,334	2,230,298	250,921	107,342	1,972,470	2,330,733
Tuberculosis	1,909	1,704	89,801	93,414	2,399	3,109	105,063	110,571
Sexually transmitted diseases (STD)	36,473	11,742	99,752	147,967	36,656	12,694	110,606	159,956
Topical microbicides	49,211	2,213	1,983	53,407	56,082	1,841	2,588	60,511
Toxic shock syndrome	477	0	0	477	690	0	0	690
Tropical diseases	5,188	4,337	303,673	313,198	4,179	7,833	462,099	474,111
Other	1,724	26,636	1,454,405	1,482,765	1,449	3,424	1,562,684	1,567,557
Subtotal	**353,865**	**151,713**	**3,815,948**	**4,321,526**	**352,376**	**136,243**	**4,215,510**	**4,704,129**
Immune Disorders								
Arthritis	$39,957	$9,577	$238,843	$288,377	$49,120	$9,480	$229,279	$287,879
Lupus erythematosus	64,608	2,004	24,600	91,212	57,181	1,231	24,819	83,231
Multiple sclerosis	18,589	10,441	65,047	94,077	14,439	8,428	71,240	94,107
Myasthenia gravis	487	429	3,288	4,204	611	551	2,497	3,659
Scleroderma	9,337	0	1,523	10,860	9,180	0	676	9,856
Sjögren's syndrome	780	0	347	1,127	776	0	120	896
Takayasu disease	0	0	0	0	0	0	0	0
Other	831	14,000	169,866	184,697	776	2,394	330,372	333,542
Subtotal	**134,589**	**36,451**	**503,514**	**674,554**	**132,083**	**22,084**	**659,003**	**813,170**
Neurologic, Muscular, and Bone								
Trauma research	10,480	13,262	159,206	182,948	10,390	12,097	170,644	193,131
Muscular dystrophy	3,393	21,115	7,875	32,383	3,317	19,389	8,978	31,684
Chronic pain conditions	9,721	8,643	64,285	82,649	9,690	9,516	79,990	99,196
Temporomandibular disorders	563	0	330	893	1,286	0	755	2,041
Fibromyalgia & eosinophilic myalgia	6,537	164	359	7,060	7,046	622	46	7,714
Migraine	1,522	1,936	1,864	5,322	1,412	1,878	1,793	5,083
Sleep disorders	4,949	4,112	38,609	47,670	4,441	4,445	41,145	50,031
Paget's disease	0	0	2,750	2,750	0	0	2,566	2,566
Parkinson's disease	19,418	21,628	128,747	169,793	19,567	21,096	124,218	164,881
Seizure disorders	22,687	20,518	44,451	87,656	19,630	18,560	55,920	94,110
Other	35,429	40,675	651,579	727,683	37,304	41,105	705,010	783,419
Subtotal	**114,699**	**132,053**	**1,100,055**	**1,346,807**	**114,083**	**128,708**	**1,191,065**	**1,433,856**

Kidney and Urologic								
Urinary tract infections	9,305	0	3,474	12,779	10,055	203	5,273	15,531
ESRD and transplantation	1,425	1,462	113,119	116,006	3,808	4,024	101,245	109,077
Urinary incontinence (cystitis, pyelonephritis)	8,830	0	500	9,330	13,783	0	1,052	14,835
Other	20,869	0	193,517	214,386	25,365	7,741	201,295	234,401
Subtotal	**40,429**	**1,462**	**310,610**	**352,501**	**53,011**	**11,968**	**308,865**	**373,844**
Ophthalmic, Otolaryngologic, and Oral Health								
Eye diseases and disorders	17,261	14,286	635,419	666,966	14,560	14,616	645,300	674,476
Ear diseases and disorders	12,511	0	330,990	343,501	13,158	0	343,238	356,396
Dental and oral health	26,437	37,286	265,400	329,123	186	0	10,097	10,283
Other	124	0	12,786	12,910	20,986	42,249	280,038	343,273
Subtotal	**56,333**	**51,572**	**1,244,595**	**1,352,500**	**48,890**	**56,865**	**1,278,673**	**1,384,428**
Health Effects of the Environment								
Environmental estrogens	11,156	380	12,469	24,005	11,010	439	21,624	33,073
Health effects of toxic exposure (excluding cancer)	517	622	61,658	62,797	219	383	49,164	49,766
Toxicological research and testing program	720	1,033	103,942	105,695	267	523	87,486	88,276
Chemical and biological warfare agents	0	0	10,724	10,724	0	0	13,792	13,792
Other	0	0	50,768	50,768	0	0	3,012	3,012
Subtotal	**12,393**	**2,035**	**239,561**	**253,989**	**11,496**	**1,345**	**175,078**	**187,919**
Cross-cutting Categories and Special Initiatives								
Treatment, prevention, and services	5,307	4,214	220,544	230,065	6,903	3,495	262,723	273,121
Access to health care and financing	173	1	3,254	3,428	446	29	5,200	5,675
Education and training for health care providers	11,104	29	10,165	21,298	791	51	9,560	10,402
Health literacy and bilingual information	0	0	14,746	14,746	0	0	18,961	18,961
Cultural influences	702	79	5,954	6,735	45	58	6,930	7,033
Disability research and services	1,997	9,195	53,240	64,432	1,990	8,288	55,906	66,184
Homelessness	743	0	1,129	1,872	251	0	1,144	1,395
Chronic fatigue syndrome	1,370	332	1,754	3,456	601	266	2,391	3,258
Breast feeding	0	0	292	292	0	0	219	219
Organ donation	0	0	655	655	0	0	0	0
Genetic services and counseling	0	0	0	0	0	0	1	1
Unintentional injury	0	0	16,853	16,853	0	0	19,663	19,663
Alternative and complementary therapies	32,012	22,588	81,057	135,657	30,298	21,404	101,091	152,793
Health statistics and data collection	0	0	6,672	6,672	25	25	2,019	2,069
Office of Women's Health	11,309	0	0	11,309	15,352	0	0	15,352
Other cross-cutting	209	301	2,356,786	2,357,296	0	27	2,468,396	2,468,423
Subtotal	**64,926**	**36,739**	**2,773,101**	**2,874,766**	**56,702**	**33,643**	**2,954,204**	**3,044,549**
Woman's and Men's Health TOTAL	**$3,498,207**	**$1,489,619**	**$20,851,094**	**$25,838,920**	**$3,478,203**	**$1,572,719**	**$22,234,583**	**$27,285,505**

* These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas.

Table 29

NIH Research Budget Summary by Gender, FY 2003 and 2004 *(Dollars in thousands)*

	Women		Men		Both*		Total	
FY	*Dollars*	*Percent*	*Dollars*	*Percent*	*Dollars*	*Percent*	*Dollars*	*Percent*
2003	$3,498,207	13.5	$1,489,619	5.8	$20,851,094	80.7	$25,838,920	100
2004	3,478,203	12.7	1,572,719	5.8	22,234,583	81.5	27,285,505	100

*Excludes the expenditures in the columns for "women" and "men." Includes research that equally and inseparably benefits men and women alike, for example, many basic research studies or clinical studies that include both women and men.

(3) For research on diseases, disorders, or conditions that affect both women and men:

a) When it can be readily determined what amount may be allocated to women or to men, those amounts should be entered in the appropriate columns. Examples would include clinical research studies where enrollment data or prevalence data give an accurate picture of the respective benefit of the study for women and men.

b) When the amount that may be allocated to men and women cannot be readily determined, the total amount may be entered in the column listed "both." Examples would include many basic research studies, research that is exploring the role of sex and gender differences, and clinical research on diseases, disorders, and conditions that affect both women and men.

For studies on diseases, disorders, or conditions that are unique to women, budgetary reporting is relatively straightforward. In contrast, for diseases, disorders, or conditions that affect both women and men, the most appropriate way to report expenditures continues to be debated. For example, the proportion of expenditures that should be considered to support research on women's health in clinical studies on lung cancer or heart disease may be determined by the proportion of women enrolled in such studies or by the relative prevalence of a condition in women. In other types of research, such as basic research studies, it may be impossible to determine what proportions of the total expenditure should be reported for women or men. Each institute and center applied the criteria according to its discretion and judgment of applicability of a single criterion or combinations of criteria. ORWH and its advisory and coordinating committees, being aware of possible inconsistencies in the evolving methods for collecting budget data, will continue to carefully monitor the outcomes and will continue to coordinate with the DHHS coordinating committee's efforts to develop the best method possible for budget data collection.

Table 28 lists the overall NIH expenditures in FY 2003 and 2004 for specific diseases, disorders, and conditions. The health categories and subcategories in Table 28 were developed to accommodate all agencies in DHHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table shows a "0" across all columns. In some cases, however, a "0" is shown even when the subcategory is appropriate. This occurs because each budget allocation may be listed only once, even though conceptually it applies to more than one category. For example, expenditures for research on infertility are listed under "female reproductive physiology" and "male reproductive disorders."

As shown in Table 29, for FY 2003 and 2004, approximately 80.7 and 81.5 percent, respectively, of the NIH budget supported research that benefits both women and men. The total actual dollars in the research budget expended on both women's and men's health, as interpreted by the specific parameters for this data collection, increased from FY 2003 to FY 2004, although the percent of total research dollars remained the same for both.

It is obvious from data compiled that the greater part of NIH expenditures is on research that benefits both men and women alike. In both FY 2003 and FY 2004, an average of 81 percent was spent on research that was not gender-specific, but that addressed health or scientific issues that affect both women and men.

For sex/gender-specific research during FY 2003, 13.5 percent and, in FY 2004, 12.7 percent of the NIH research budget was spent on women's health research, while 5.8 percent for both FY 2003 and 2004 was spent on men's health research. These differences are most likely due to the fact that there are more sex/gender-specific conditions that affect females, such as menarche, menopause, reproduction, and gynecologic neoplasms, than there are male-specific conditions and diseases.

Executive Summary

Overview

The scope and expansion of Women's Health Research across the NIH has been remarkable over the past 2 years. This report is evidence of the progress that has been achieved and readers are encouraged to review the detailed IC reports that discuss the important advances in understanding about women's health research that have been achieved in the last 2 years.

Cancer continues to take a devastating toll on American women, but important progress is being achieved in the fight against cancer overall, and specifically for women. Cancer incidence rates for all cancers in women have recently declined slightly. Mortality rates have decreased for all cancers combined in the general population, and for eight of the top 15 cancers in women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after increasing for many decades. Five-year cancer survival rates have improved since the late 1970s, although less significantly for women than for men. In addition to the extensive research supported at the NCI and through research grants, a number of specific programs and activities in the NCI focus on women's cancers, including the Breast and Gynecologic Cancer Research Group, the Breast Cancer Surveillance Consortium, the Gynecologic Oncology Group, the Breast and Gynecologic Malignancies Faculty, and the HPV (human papillomavirus) Working Group. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. These programs address cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. These cancers include breast, cervical, ovarian, endometrial, colorectal, and lung and other tobacco-related cancers, as well as malignancies associated with acquired immunodeficiency syndrome (AIDS).

The NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. It plans and conducts, through work in its own laboratories and through grant- and contract-supported activities in extramural scientific institutions, an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of the diseases under its purview and to the clinical use of blood and all aspects of the management of blood resources. The NHLBI also supports a variety of educational programs for physicians, patients, and the general public to improve awareness, diagnosis, treatment, and prevention of diseases and conditions under the institute's purview. Since FY 1993, the institute has been the home of the National Center on Sleep Disorders Research and, since FY 1998, it has had responsibility for the NIH Women's Health Initiative (WHI).

The NIAID conducts and sponsors research focused on the diagnosis, treatment, and prevention of infectious diseases, as well as disorders of the immune system. Many of these diseases and disorders adversely affect women, including the human immunodeficiency virus (HIV), which causes AIDS, and other sexually transmitted infections (STIs). In a continual response to the global prevalence of HIV/AIDS, and the frequency of heterosexual and perinatal transmission, the NIAID continues its commitment to support studies on HIV/AIDS in women. Ongoing natural history cohort studies and HIV/AIDS clinical trial networks have expanded their

research on HIV/AIDS to: investigate the etiology and pathogenesis of HIV/AIDS in women; the effectiveness of topical microbicides; and other promising approaches to decrease sexual transmission, improve treatment of HIV/AIDS in women, and support perinatal AIDS-related research. STIs are critical global and national health priorities because of the devastating impact on women and infants, and the interrelationships with HIV/AIDS. STIs and HIV are linked by biological interactions and infections occurring in the same populations. Infection with certain STIs can increase the risk of HIV acquisition and transmission, as well as alter the course of disease progression. The NIAID also addresses immune-mediated diseases, including asthma and allergic diseases and the immune-mediated rejection of transplanted solid organs, tissues, and cells.

The NIDDK conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematological diseases. Within the NIDDK research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include: gestational diabetes; obesity (especially in racial and ethnic minority populations); coronary artery disease; cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome and other functional gastrointestinal disorders; osteoporosis; thyroid diseases; hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis; urinary tract infections; urinary incontinence; and lupus nephritis. Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease. Obesity is increasing dramatically in the U.S. population and is now considered an epidemic. The problem is particularly severe for African American, Hispanic/Latino American, and American Indian women. The NIDDK supports research that directly addresses the important women's health questions cited above, both through basic research directed to understanding underlying disease processes, and through clinical research that translates this understanding into therapies and preventive interventions.

The NIA conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. NIA-supported researchers made important progress in a number of women's health-related areas, including Alzheimer disease where investigators have reported new findings regarding the risks and benefits of hormone therapy with regard to cognition, identified a potential link between diabetes and cognitive decline in postmenopausal women, and continued to seek ways to reduce the burden on care givers of chronically ill patients. The NIA has several ongoing research initiatives dealing specifically with women's health. These include the Study of Women's Health Across the Nation (SWAN). The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in women of various racial/ethnic backgrounds. An additional research project is the Women's Health Initiative Study of Cognitive Aging (WHISCA), which is an ancillary project of the Women's Health Initiative Memory Study and the Women's Health Initiative (WHI). Since 1999, WHISCA has investigated the effects of hormonal therapy on longitudinal changes in memory and specific cognitive functions in older non-demented WHI participants. In addition, the NIA is currently supporting an extensive program of research pertaining to health disparities among special populations. Much of this research is relevant to the health concerns of minority women.

The NICHD research aims to overcome many of the complex challenges that face women, in addition to their children and families, including research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are key to improving the quality of life for women. Research is also shedding light on how fibroids form, providing scientists with the preliminary

knowledge that they need to begin developing non-surgical treatments for a condition that affects millions of women. Other research has found substances in blood that may predict preeclampsia in pregnant women, a complication that can be fatal. The full extent of this finding may be realized in future research leading to the development of treatments that can prevent or treat the condition before it becomes life threatening, saving the lives of thousands of women. Through the Maternal Fetal Medicine Units Network, researchers showed the remarkable effectiveness of a new progesterone treatment that reduces the risk of preterm birth in women who previously gave birth at less than 37 weeks. This is one of the first major discoveries in this area, despite extensive efforts over decades, and promises to help change obstetrical practice.

NINDS focuses on reducing the burden of neurological disease, a burden borne by every age group, by every segment of society, and by people all over the world. Most nervous system disorders affect men and women equally, but certain disorders are more prevalent in, or are of special interest to, women, such as multiple sclerosis (MS), pain, stroke, and epilepsy. Hormonal factors may influence MS, with some forms of MS about twofold more frequent in women, and fewer relapses are reported during pregnancy. Other research focuses on MS biomarkers, and to better understand the genetic, hormonal, and environmental contributions to MS. Additionally, some chronic pain conditions, like migraine headaches or fibromyalgia, tend to be diagnosed more often in women than in men, so it is important to understand pain pathways and mechanisms of pain processing, modulation and regulation, and pain management. The NINDS also supports research on strokes, a major cause of disability in both women and men. Although women in general have a lower risk of stroke than men because of their longer life expectancy, they account for 60 percent of stroke fatalities. This program ranges from basic investigation of stroke mechanisms through large studies of risk factors and clinical trials aimed at prevention and treatment. Research is also targeted to special issues of stroke in various populations, including women. One such study is examining the risk of stroke in patients with systemic lupus erythematosus (SLE).

The NIAMS supports research on a number of diseases that disproportionately affect women, including osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint disorders (TMJ), fibromyalgia, and systemic lupus erythematosus (lupus). Lupus is a disease in which health disparities have been clearly identified. The NIAMS has continued to develop the Osteoarthritis Initiative and has launched the Osteoarthritis Biomarkers Network, a program designed to hasten the pace of discovery of molecular biomarkers for osteoarthritis. Scientists have long suspected that autoimmune diseases, such as rheumatoid arthritis, result from a combination of genetic and environmental factors, and researchers have recently identified a genetic variation that appears to double rheumatoid arthritis risk. Lupus is another autoimmune disease, and treatment often involves powerful drugs that suppress the immune system. Researchers have found a potential treatment to suppress the abnormal, self-directed immune response that is responsible for lupus without hampering the body's ability to fight bacteria and viruses. Other researchers have also determined that people with lupus may develop fatty deposits in their arteries at an accelerated rate and show autoantibodies in their blood years before the symptoms of lupus appear.

The NIDA has made a major effort to investigate issues specific to women and to study sex/gender differences. The major goal of this effort is to infuse the study of sex/gender differences and issues specific to females in all areas of drug abuse research and to disseminate research findings in this area. Basic research on the biological underpinnings and consequences of drug abuse is informing field research on etiology and consequences of drug abuse. Research on prevention and treatment is increasing and includes a sex/gender-based research approach to analyze data separately for males and females. This research is repeatedly showing that sex/gender matters in drug abuse. NIDA-supported research

findings fall into six major research areas: biological mechanisms and consequences, prenatal exposure to drugs, nicotine addiction, adolescents, treatment and treatment services, and HIV/AIDS. These findings strongly suggest that the identification and understanding of sex/gender differences can improve our understanding of the nature, etiology, and consequences of drug abuse and that it may have implications for tailoring prevention and treatment interventions to maximize outcomes for both males and females.

Within NIEHS-supported research, environmental agents likely play a role in a number of important female-predominant diseases—breast cancer, osteoporosis, ovarian dysfunction (e.g., premature menopause, polycystic ovarian syndrome, and ovarian cancer), uterine fibroids, and autoimmune diseases. The approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds (both natural and synthetic) in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to determine the importance of the timing of exposure on disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases, and environmental health regulators can better define standards that protect women from environmental triggers of these diseases.

Prevention and intervention efforts are major focuses of the NIEHS activities. These efforts include hazard identification and characterization, both through traditional animal testing and epidemiologic studies and through incorporation of mechanistic considerations to arrive at new insights into the molecular basis of toxic effects. Although many people think of environmental exposures in terms of synthetic chemicals, the NIEHS also investigates natural compounds and the importance of diet and supplements in protecting health. Identifying important triggers of disease is complicated by the fact that environmental exposures do not act in isolation. Underlying genetic susceptibilities, as well as the stage of life at which exposures occur, can have a profound effect on final disease risk. The NIEHS continues to investigate genetic susceptibilities to environmental disease risk and is spearheading the Environmental Genome Project that will help identify the important genetic variants of environmental response genes for both women and men.

Through research supported by the NIMH, the epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders than boys. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including post-traumatic stress disorder. There are also differences in the course and severity of mental disorders between men and women. For example, men have an earlier average age of onset of schizophrenia, while women are more likely to suffer from the rapid cycling form of bipolar disorder. Additionally, women are at increased risk of recurrence of depression during certain times of reproductive change, such as in the perinatal period. Findings from areas of basic and clinical neuroscience, epidemiology and risk factors, and intervention development are grouped by five major subheadings: developmental aspects of sex and gender differences; mood and anxiety disorders; eating disorders; schizophrenia and other serious mental disorders; and health behavior, AIDS, and mental health disparities.

The NCCAM conducts basic and applied research and research training in the five major domains of complementary and alternative medicine (CAM): 1) whole medical systems, such as traditional Chinese medicine; 2) mind-body medicine; 3) biologically based practices, such as herbal therapies; 4) manipulative and body-based practices, such as chiropractics; and 5) energy medicine. CAM therapies for women treat a variety of conditions, such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and urinary tract problems.

The NCCAM also as a strong interest in menopausal health, and working with other ICs has developed a multi-pronged approach to improving our knowledge of CAM for the treatment of menopausal symptoms, convening workshops, producing reports, and supporting research and research training. These include assessing the quality of measures of hot flashes, which is important to assess treatment efficacy, and ways to improve sternal skin conductance technologies. NCCAM also supports a range of pain-related research to addresses diseases such as fibromyalgia and arthritis, which differentially affect women, and include the mechanism of action of acupuncture, CAM interventions to treat osteoarthritis symptoms. Other relevant work in the area of pain pertains to the safety and efficacy of several botanicals purported to have anti-inflammatory action, a broad range of research projects on CAM therapies for cancer treatment, including a number of botanicals, acupuncture, healing touch, and mushroom extracts.

The NIAAA-supported research confirms that women represent 4 of the 14 million alcohol-abusing or alcohol-dependent individuals in the United States. Women drink less alcohol and have fewer alcohol-related problems and dependence symptoms than men, but among the heaviest drinkers women equal or surpass men in the problems that occur because of their drinking. The NIAAA continues to expand its research portfolio on the impact of alcohol and alcohol misuse on women, and has increased the understanding of the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women. Research on women (including gender-based differences) was addressed by six central themes: 1) psychosocial determinants of drinking in women; 2) violence and other social consequences of alcohol misuse; 3) impact of alcohol use and misuse on women's physiology; 4) drinking during pregnancy; 5) treatment of women with alcohol use disorders; and 6) biobehavioral correlates of alcohol use and misuse in women. Research in the area of genetics is consistently revealing differences at the molecular level that helps to explain gender differences in the rates of alcohol dependence and other psychiatric disorders. Studies evaluating approaches to preventing fetal alcohol spectrum disorders have shown an acceptance of alcohol screening and brief interventions among women attending obstetric clinics.

The NINR supports clinical and basic research to establish a scientific basis for the care of individuals across the life span. The focus of women's health studies has often centered on reproductive function. However, emerging models of health care services need to address all circumstances of women's health across the life span. Nursing has a long tradition of concern for the health of women and of developing and providing services oriented to the needs of women. Investigators and nurse scientists supported by the NINR have contributed new knowledge addressing women's health related to cardiovascular health, midlife and menopause, aging, cultural and ethnic variations, HIV/AIDS, cancer, chronic disease, women as care givers, and other related issues. In addition, the NINR continues a strong reproductive health research program through studies that focus on care during pregnancy and delivery, maternal issues in infant care and child development, and adolescent sexuality and pregnancy. The NINR supports initiatives related to its strategic plan on reducing health disparities, including research on various aspects of health during pregnancy for minority populations.

The NEI supported research that confirmed that several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, dry eye, associated with decreased tear secretion that in most cases causes mild discomfort but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, progressive corneal distortion, and corneal scarring; and age-related macular degeneration, a deterioration of the region of the retina that is responsible for high-resolution vision.

The NIDCR supports research in areas as diverse as understanding the oral infections that lead to dental decay, periodontal disease, and recurrent herpes lesions; oral manifestations of osteoporosis and other

bone disease; salivary gland dysfunction and disease; and connective tissue diseases and disorders. Because one-quarter of all chronic pain is associated with the face and mouth, the NIDCR has become a leader in the field of pain research. Research advances that affect women include chronic pain, TMJ, osteoporosis and basic bone biology, cancers, autoimmune disease, HIV infection, health disparities, craniofacial anomalies and periodontal diseases, and systemic effects. Pain conditions, including those that primarily affect women, have been an active area of NIDCR-supported research for a number of years. Findings from studies indicate that gender-based differences in pain conditions are due, in part, to biological differences between women and men.

The NIDCD is supporting a number of diseases, disorders, or conditions that affect women disproportionately. For example, cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of sensorineural hearing loss per year. Gestational diabetes is a common complication of pregnancy that requires special attention to diet to insure proper maternal and child health. Research has shown that gestational diabetes can adversely affect nutrition by increasing the preference for and intake of sweet-tasting foods. A greater proportion of women than men with MS show olfactory loss, and the loss is more profound in women.

The FIC's research and research training programs address a wide range of topics of concern to the global health community, including infectious diseases, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, population dynamics, environmental and occupational health, bioethics, trauma and injury, tobacco control, and biodiversity. Many of the FIC's research training programs include activities aimed at improving women's health. In particular, the FIC supports research training in reproductive processes; contraceptive development; and demographic studies of population health issues, including rapid societal changes, societies under stress, and aging. The FIC also supports research training to address the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The FIC funds training for research to address issues of HIV infection, many of which have particular relevance for women: stigma associated with HIV/AIDS, perinatal transmission of HIV, HIV transmission through breast feeding, and female-controlled methods to reduce sexual transmission of HIV (including microbicides, biomedical interventions, and behavioral interventions). The FIC also supports a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world, and provides the opportunity for a wide spectrum of research on women's health problems and issues. Some examples of areas of research supported by the FIRCA program that include women are obesity, smoking cessation, and cervical and breast cancers.

The NCRR supports basic and clinical research on prevention and treatment of diseases, disorders, or conditions that are unique to women or have a significant impact on women, including research that promotes understanding of normal and abnormal physiology in women. Accomplishments include research from centers dedicated to women's health, a mentorship program in women's health, animal models and biological materials, programs that focus on health disparities for minority women, and individual research projects on a variety of health issues related to women.

The NHGRI led the NIH contribution to the International Human Genome Project. With the achievement of its final goal, the finished sequence of the human genome, this project has already begun to change the way we address research on women's health. The NHGRI has moved forward into the genomic era with a wide range of powerful new extramural research initiatives that will accelerate genome research and its application to human health, including the role of the BRCA1 and BRCA2 gene in

the pathogenesis of breast cancer. The NHGRI supports a new study of breast cancer families that do not have mutations in either the BRCA1 or BRCA2 genes to identify other genes that are involved in breast cancer. Hereditary nonpolyposis colorectal cancer is a hereditary cancer syndrome that includes cancer risks for colon, endometrial, ovarian, stomach, small intestine, gall bladder, urinary tract, brain, and rarely pancreas. Woman in these families may have as high a risk for endometrial cancer as they do for colon cancer.

The NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. Most studies supported by NIGMS do not target any particular disease or condition, but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. Often basic research supported by the Institute will result in findings pertinent to women's health. A basic understanding of the etiology of a disease, the predisposing factors and the cellular processes involved, and the mechanisms that promote disease progression are necessary for prevention, early diagnosis, and effective treatment of disease. The NIGMS support of fundamental research impacts on virtually all these areas, and supports interdisciplinary research training at the predoctoral and postdoctoral levels.

The NIBIB is the newest of the research institutes within the NIH. As the NIBIB continues to grow and structure programs, new initiatives are in development to support a variety of scientific areas, including programs aimed at fostering women's health research. The NIBIB recognizes the significant potential of improved imaging technologies in early disease detection, including those focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women's diseases, such as breast cancer, and disorders and conditions that predominate in women, including osteoporosis and TMJ. Increased support of other women's health research also occurred in the following disease areas: aging, autoimmune disease, cervical cancer, contraception/reproduction, diabetes and diabetes research, epilepsy, HIV/AIDS, heart disease, lung cancer, stroke, and TMJ.

Highlights of Institute and Center Activities

Fogarty International Center

The Fogarty International Center (FIC), the international component of the NIH, addresses global health challenges through innovative and collaborative research and training programs and supports and advances the NIH mission through international partnerships.

The FIC's research and research training programs address a wide range of topics of concern to the global health community, including infectious diseases, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, population dynamics, environmental and occupational health, bioethics, trauma and injury, tobacco control, and biodiversity.

Many of the FIC's research training programs include activities aimed at improving women's health. In particular, the FIC International Research and Training Program in Population and Health supports research training in reproductive processes; contraceptive development; and demographic studies of population health issues, including rapid societal changes, societies under stress, and aging. The FIC International Maternal and Child Health Research and Training Program supports research training to address the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The FIC AIDS International Training and Research Program funds training for research to address issues of HIV infection, many of which have particular relevance for women: stigma associated with HIV/AIDS, perinatal transmission of HIV, HIV transmission through breast feeding, and female-controlled methods to reduce sexual transmission of HIV (including microbicides, biomedical interventions, and behavioral interventions). The Fogarty International Research Collaboration Award (FIRCA), a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world, provides the opportunity for a wide spectrum of research on women's health problems and issues. Some examples of areas of research supported by the FIRCA program that include women are obesity, smoking cessation and cervical and breast cancer.

In FY 2002, the FIC launched the Stigma and Global Health Research Program in partnership with several other NIH Institutes and with the ORWH. The first awards under this program were made in FY 2003, and address the role of stigma in health, and on how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups, and societies worldwide. Research projects supported by this program study how stigma associated with specific health conditions interacts with individual or group characteristics (such as gender, race, religion, sexual orientation, and nationality). Some projects are specifically focused on linkages between gender, stigma and health, including AIDS stigma and gender discrimination in urban Indian health care systems; culture, gender and healthcare stigma in Parkinson's disease in Taiwan; and stigma, gender, and risk behaviors in school youth.

National Cancer Institute

Cancer continues to take a devastating toll on American women. In 2005, an estimated 662,870 women will have been diagnosed with cancer, and approximately 275,000 women will have died of the disease.* Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. Cancer incidence rates for all cancers in women have recently declined slightly. Mortality rates have decreased for all cancers combined in the general population, and for eight of the top 15 cancers in

* Incidence and mortality statistics reported for 2003 and after are age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from the 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, were changed as the new statistics were calculated. A complete summary can be found at: *http://www.cancer.gov/newscenter/pressreleases/Census2000*.

women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after increasing for many decades. Five-year cancer survival rates have improved since the late 1970s, although less significantly for women than for men.

The National Cancer Institute (NCI) is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. Through its strategic planning process, the NCI identifies many of the questions that need to be answered, areas of research and care that need to be supported, and infrastructure that needs to be strengthened, to ultimately eliminate the suffering and death due to cancer (see *http://plan2006.cancer.gov*). The NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported at the NCI and through research grants, a number of specific programs and activities in the NCI focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group clinical trials cooperative group in the Division of Cancer Treatment and Diagnosis, and the Breast and Gynecologic Malignancies Faculty and the HPV (Human Papillomavirus) Working Group in the Center for Cancer Research. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application.

This report describes many of the activities and accomplishments of the NCI's research programs in fiscal years 2003 and 2004, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

Biology, Genetics, and Cancer Risk

To develop more effective approaches to cancer prevention, early detection, and treatment, a better understanding of the molecular mechanisms that lead to cancer development and progression is required. In addition, the identification and interactions between inherited genetic and environmental factors that increase cancer risk is critical. For example, the NCI supports research to develop and apply animal models of human cancers, identify genetic and proteomic factors associated with cancer development and progression, and elucidate molecular interactions among cancer cells and their microenvironment. The NCI supports consortia and networks to pool the resources of multidisciplinary researchers for large population studies that explore genetic and environmental risk factors. For example, the NCI Consortium of Cohorts conducts large-scale collaborations for study of gene-gene and gene-environment interactions in the cancer etiology. The NCI is supporting large cohort studies in Costa Rica and the United States to better define risk factors for progression of precancerous lesions among HPV-infected women. The Cancer Genetics Network Colon Sibling Pair study seeks to identify genetic and environmental factors involved in the development of colorectal cancer.

Cancer Prevention Research

Researchers are applying their knowledge about cancer risk to develop cancer prevention strategies. For example, the NCI and partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. Researchers are investigating selective estrogen receptor modulators and aromatase inhibitors for use in breast cancer prevention and cholesterol-lowering statins for colorectal cancer prevention. Other researchers are also identifying dietary and behavioral factors that can help prevent different types of cancer.

Early Detection

The NCI and partners are developing and applying techniques to detect cancer in its earliest, most treatable stages. Investigators

are conducting large, multisite studies of digital mammography for breast cancer screening and low-dose spiral computed tomography for lung cancer screening. A proteomics-based test for early detection of ovarian cancer is now in clinical trials. The NCI is helping to test a gene expression profiling technique to predict risk of breast cancer recurrence. Finally, NCI scientists have demonstrated that HPV DNA testing predicts increased risk for future cervical precancers and cancers.

Cancer Treatment

Research has led recently to improved regimens of traditional chemotherapeutic agents for breast, cervical, ovarian, endometrial, lung, and colorectal cancers, and AIDS-associated malignancies. New treatment modalities, such as aromatase inhibitors for breast cancer, are improving survival and quality of life for patients. Increasing knowledge of the molecular changes that cause cancer, as well as the reaction of the immune system to cancer, is enabling researchers to identify potential targets for the discovery of new targeted therapies and preventives. Molecularly targeted therapies, including monoclonal antibodies, are being developed to treat breast, endometrial, lung, and colorectal cancers. NCI researchers are also helping to develop a treatment vaccine for non-small cell lung cancer.

Cancer Health Disparities, Quality of Care, Outcomes, and Survivorship

The NCI's Center to Reduce Cancer Health Disparities provides the organizational locus for the critical tasks needed to advance understanding of the causes of cancer health disparities and to develop and integrate effective interventions to eliminate them. For example, the center has an ongoing program to understand the origins of and address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas. The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, social, and biomedical research on the interrelationships among cognition, emotion, biological processes, and physical health in patients with cancer. The NCI and partners develop and disseminate educational materials targeting minority and underserved women, addressing topics such as smoking cessation, use of mammography, and surgery choices for early-stage breast cancer. NCI-funded researchers also are assessing the effects of energy balance-related behaviors on the health and quality of life of cancer survivors.

Tobacco and Cancer

The devastating impact of tobacco use and exposure to tobacco is being addressed by studies to understand the genetic, social, behavioral, and environmental factors involved in tobacco addiction and control; assess cancer risk factors that differentially affect smokers and nonsmokers; identify behavioral and pharmaceutical interventions for smoking prevention and smoking cessation; and improve detection of and treatments for tobacco-associated cancers. A working group meeting, held in February 2003, Women, Tobacco, and Cancer: An Agenda for the 21st Century, assembled researchers, clinicians, and members of the advocacy community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. The working group released their report in July 2004, recommending strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, and evaluation and surveillance that will contribute to reducing and ultimately eliminating the harmful health effects of smoking in women.

The National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) was established through a congressional mandate under the FY 1999 Omnibus Appropriations Bill PL105-277 signed by the President in October of 1998. The mission of the 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. CAM encompasses those health care and medical practices that are not currently an integral part of conventional medicine. The list of CAM practices and therapies changes as ones are proven to be safe and effective become accepted as "mainstream" healthcare practices. NCCAM groups CAM practices within five major domains: 1) whole medical systems (i.e., traditional Chinese medicine, Naturopathic Medicine, Ayurveda); 2) mind-body medicine (i.e., meditation, biofeedback); 3) biologically based practices (i.e., herbal therapies, special diets); 4) manipulative and body-based practices (i.e., Chiropractic, massage); and 5) energy medicine (i.e., Reiki, Qi gong). NCCAM conducts and supports basic and applied (clinical) research and research training within these five areas.

The 2002 National Health Interview Survey found that 62 percent of the 31,044 respondents had used some form of CAM therapy in the past year; when prayer for health reasons was excluded from the definition, over a third (36 percent) reported use of CAM in the previous 12 months. After prayer for one's own health (43 percent), the other most common forms of CAM used were natural products (18.9 percent), deep breathing exercises (11.6 percent), meditation (7.6 percent), chiropractic care (7.5 percent), yoga (5.1 percent), massage (5.0 percent), and diet based therapies (3.5 percent). Women were more likely to use CAM than men, with the largest gender differential seen with mind-body therapies, including prayer specifically for health purposes. CAM therapies are used to treat a broad range of health conditions by both men and women, including back and neck problems, allergies, fatigue, arthritis, headaches, diabetes, and cardiovascular disease. CAM therapies for women treat a variety of conditions such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and urinary tract problems. Thus, the NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

NATIONAL CENTER FOR RESEARCH RESOURCES

The National Center for Research Resources (NCRR) has a unique responsibility at the National Institutes of Health (NIH): to serve as a "catalyst for discovery." Biomedical research investigators receiving support from the Institutes and Centers (ICs) of the NIH require a broad array of technologies, tools and materials critical to their research efforts to address health problems. Through its four divisions, the NCRR develops and supports biomedical resources that include: shared sophisticated research instrumentation; specialized animal models for studies of human diseases; flexible support mechanisms to invest in emerging research opportunities; a cost-saving nationwide network of clinical research centers; strong research infrastructure for predominantly minority institutions; infrastructure enhancement and mentorship at institutions in states with little history of NIH funding; and construction, alterations, and renovations to research facilities and animal care centers. Through its support of multidisciplinary research, the NCRR is uniquely positioned to provide funds directly for research, or to act in partnership with other NIH components, in order to address emerging clinical and basic research needs for women's health.

The Division for Biomedical Technology Research and Research Resources supports research on, development of and access to sophisticated technologies at biomedical technology resource centers. This is accomplished by providing funds for the acquisition of new state-of-the-art shared instrumentation, and by supporting special-emphasis technology development in high performance computing, molecular and cellular structural biology technologies, biomedical engineering, noninvasive imaging and spectroscopy, mathematical modeling, and computer simulations.

The Division for Clinical Research Resources provides clinical research infrastructure for medical scientists who conduct patient-oriented research. This research may be supported by the NIH or by funds provided though other federal, state, and local agencies and the private

sector. The division administers programs to increase the opportunities for clinicians to be involved in patient-oriented research; to procure and distribute a wide variety of human tissues and organs for medical research; to provide vectors for clinical trials of gene therapies; and to support meetings and workshops dedicated to understanding or treating human diseases.

The Division of Comparative Medicine provides high quality, disease-free animal models and specialized animal research facilities for biomedical investigators. Through grants, cooperative agreements, and contracts, this division supports national primate research centers and their field stations, primate breeding and resource-related projects, development of mammalian and nonmammalian animal model resources, postdoctoral training, and a variety of research projects.

The Division of Research Infrastructure expands the nation's ability to conduct biomedical and behavioral research by developing research infrastructure of all kinds. This includes support for construction and renovation of biomedical and clinical research laboratories and animal facilities, recruitment of new faculty, performance of pilot projects, and acquisition of research equipment. Support from this division is provided to predominantly minority-serving institutions that award doctorates in the health or health-related sciences, and to institutions in states that have historically had limited NIH support. This support enables junior college, baccalaureate, and masterís degree-granting institutions to significantly enhance their capacity to conduct biomedical and behavioral research by developing and strengthening formal, collaborative agreements with research-intensive, doctoral degree-granting institutions.

The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by NCRR to promote understanding of normal and abnormal physiology in women. In addition, NCRR supports research on prevention and treatment of diseases, disorders, or conditions that are unique to women or have a significant impact on women. Accomplishments include research from centers dedicated to women's health, a mentorship program in women's health, animal models and biological materials, programs that focus on health disparities for minority women, and individual research projects on a variety of health issues related to women.

National Center on Minority Health and Health Disparities

The National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads, coordinates and assesses the NIH effort to reduce and eliminate health disparities. To achieve its mission, the NCMHD employs a multi-faceted strategy to conduct and support research at the basic, clinical, social sciences, and behavioral levels; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. This report provides a summary of the breadth of the NCMHD supported national activities for fiscal years 2003 and 2004, that focus on women's health through its extramural programs and partnerships with the other NIH Institutes and Centers (ICs). The Congress mandated the development of three principal programs within the NCMHD aimed at addressing health disparities—the Loan Repayment Program, the Centers of Excellence Program, and the Research Endowment Program. Additionally, the NCMHD has a Research Infrastructure in Minority Institutions Program (RIMI) and a Minority Health and Health Disparities International Research Training Program (MHIRT) that also support its efforts to tackle the elimination of health disparities.

NCMHD Loan Repayment Program

The NCMHD has two distinct loan repayment programs: 1) The Health Disparities Research program which supports the recruitment and retention of highly qualified health professionals to conduct biomedical, clinical, behavioral, community-based, and health services research relevant to health disparities; and 2) the Extra-

mural Clinical Research program which supports the recruitment and retention of health professionals from disadvantaged backgrounds to conduct clinical research.

Centers of Excellence Program

The NCMHD's Centers of Excellence in Partnership for Community Outreach, Research on Health Disparities, and Training (Project EXPORT) program supports the establishment of Centers of Excellence to conduct research, support research training, and community outreach activities relevant to health disparities. The program seeks to advance the science related to health disparities; create, develop, and evaluate new interventions for preventing, reducing, and eliminating health disparities; and disseminate information useful for improving health via novel partnerships established between Centers of Excellence and health disparity communities.

Research Endowment Program

This NCMHD program builds research and training capacity in institutions that make significant investments in the education and training of individuals from health disparity populations. The program's goals include the promotion of research; enhancement of the ability of designated health professions schools to support program development, capital improvements, and access to emerging technology; and the recruitment and retention of qualified individuals from health disparity populations that are currently underrepresented in the scientific and health professions workforce.

Research Infrastructure in Minority Institutions Program

The Research Infrastructure in Minority Institutions Program (RIMI) supports institutions that enroll a significant number of students from minority health disparity populations to develop and enhance their capacity and their competitiveness to conduct biomedical research. The RIMI program also assists nondoctoral degree institutions to develop their research infrastructure, primarily through collaborations with research-intensive universities.

Minority Health and Disparities International Research Program

The Minority Health and Disparities International Research Program (MHIRT) was designed to enable U.S. institutions to offer short-term international research training opportunities for qualified eligible students in basic science, biomedical, clinical or behavioral research to address global issues related to eliminating health disparities.

The NCMHD also has responsibility for developing and overseeing the implementation of the NIH Health Disparities Strategic Plan which consists of the 5-year strategy and accompanying budget for combating health disparities for all of the NIH ICs in light of their respective missions. These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities to benefit all affected populations including women of diverse populations. In addition to the highlights of the NCMHD programs that follow, a noteworthy accomplishment for the NCMHD and the NIH in fiscal year 2004, was the establishment of a new definition for minority health and health disparities and consistent guidelines that the ICs would apply when reporting on minority health and health disparities activities. The new definition for health disparity populations now includes low socioeconomic status and rural populations. This was the result of the work of the NIH Committee on Minority Health and Health Disparities Research Definitions and Application Methodology.

NATIONAL EYE INSTITUTE

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and

men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States.

Several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion that in most cases causes mild discomfort but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, a slowly progressive disease that occurs when endothelial cells deteriorate as a result of cell loss, age, or trauma-induced keratoconus, a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring; and age-related macular degeneration, a deterioration of the region of the retina that is responsible for high-resolution vision.

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. It plans and conducts, through work in its own laboratories and through grant- and contract-supported activities in extramural scientific institutions, an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of the diseases under its purview and to the clinical use of blood and all aspects of the management of blood resources. For more than 30 years, the NHLBI Office of Prevention, Education, and Control has supported educational programs for physicians, patients, and the general public to improve awareness, diagnosis, treatment, and prevention of diseases and conditions under the institute's purview. Since FY 1993, the institute has been the home of the National Center on Sleep Disorders Research and, since FY 1998, it has had responsibility for the NIH Women's Health Initiative (WHI).

Highlights of NHLBI-supported activities during fiscal years 2003 and 2004 include the following:

- The WHI postmenopausal hormone component reported the main outcome of its trial of estrogen in women with a hysterectomy. Other publications provided detailed information about the effects of estrogen stroke plus progestin on health-related quality of life, gynecologic cancers, bone health, and colorectal cancer.
- The Women's Ischemia Syndrome Evaluation (WISE) Study, which has been examining issues of relevance to diagnosis of chest pain and myocardial ischemia in women, produced a number of new findings regarding predictors and correlates of cardiovascular disease (CVD) risk.
- The NHLBI women's heart health education campaign, titled The Heart Truth, greatly expanded its activities to raise public awareness that heart disease is the leading cause of death among women in the United States, and that many things can be done to prevent it.

National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) led the National Institutes of Health's (NIH) contribution to the International Human Genome Project (HGP). With the achievement of its final goal, the finished sequence of the human genome in April 2003, this project was successfully completed ahead of schedule and under budget, and has already begun to change the way we address research on women's health.

In October 2004, the International Human Genome Sequencing Consortium, led in the United States by the NHGRI and the Department of Energy, published an analysis of that finished human genome sequence in the journal *Nature*. This analysis

reduces the estimate of the number of human protein-coding genes from 35,000 to only 20,000 to 25,000—a surprisingly low number for our species, considering that only a decade ago most scientists thought we had over 100,000 genes.

The NHGRI has moved forward into the genomic era with a wide range of powerful new extramural research initiatives that will accelerate genome research and its application to human health. The NHGRI also supports research to study the ethical, legal, and social implications of genomic research, known as "ELSI." The ELSI program at the NHGRI is the largest supporter nationwide of ELSI research. As well, in its Division of Intramural Research (DIR) scientists are using the techniques and tools produced by the HGP—and developing new ones—to study the fundamental mechanisms of inherited and acquired genetic disorders, including many disorders that are more prevalent in women, to lead ultimately to improved diagnostic, prevention, and treatment strategies.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases (NIAID) stands at the forefront of scientific research on a number of diseases that threaten the survival and quality of life of millions of people. The NIAID conducts and sponsors research focused on the diagnosis, treatment, and prevention of infectious diseases, as well as disorders of the immune system. Many of these diseases and disorders adversely affect women, including the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), and other sexually transmitted infections (STIs). The NIAID also addresses immune-mediated diseases, including asthma and allergic diseases and the immune-mediated rejection of transplanted solid organs, tissues, and cells.

In a continual response to the global prevalence of HIV/AIDS, and the frequency of heterosexual and perinatal transmission, the NIAID continues its commitment to support studies on HIV/AIDS in women. Ongoing natural history cohort studies and HIV/AIDS clinical trial networks have expanded their research on HIV/AIDS to investigate the etiology and pathogenesis of HIV/AIDS in women; the effectiveness of topical microbicides; and other promising approaches to decrease sexual transmission and improve treatment of HIV/AIDS in women.

The NIAID also supports perinatal AIDS-related research, and furnishes necessary information to: 1) design clinical trials for HIV/AIDS-infected pregnant women and children; 2) improve methods for detecting maternal–fetal retroviral transmission in human and animal models; and 3) prevent HIV/AIDS transmission from pregnant mothers to their babies. Based on preclinical research, NIAID is evaluating new therapies and approaches for the prevention of perinatal transmission both domestically and internationally. Through the Pediatric AIDS Clinical Trials Group (PACTG), which is co-funded by the National Institute for Child Health and Human Development (NICHD), the NIAID continues to evaluate treatments for HIV/AIDS-infected children and adolescents.

STIs are critical global and national health priorities because of the devastating impact on women and infants, and the interrelationships with HIV/AIDS. STIs and HIV are linked by biological interactions and infections occurring in the same populations. Infection with certain STIs can increase the risk of HIV acquisition and transmission, as well as alter the course of disease progression. Recent studies indicate that the more prevalent non-ulcerative STIs (chlamydial infection, gonorrhea, bacterial vaginosis, and trichomoniasis), as well as the ulcerative diseases (genital herpes, syphilis, and chancroid), increase the risk of HIV transmission by at least two- to fivefold. In addition, STIs can cause long-term health problems, particularly in women and infants. Some of the sequelae of STIs include: pelvic inflammatory disease (PID); infertility; fetal wastage; low birth weight; congenital/perinatal infection; chronic conditions, such as neurosyphilis, tubal, or ectopic pregnancy; cervical cancer; increased risk of HIV infection; and

perinatal or congenital infections in infants born to infected mothers.

In summary, the NIAID is continuing its activities in these diverse, but interrelated, areas of investigation, building on past findings and exploiting new scientific opportunities as they arise. The Office of Special Populations and Research Training (OSPRT), NIAID, is the coordination point for reporting the NIAID's research on women's health. This report provides an overview of the major accomplishments and initiatives within the Institute that address women's health research.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting Americans. The NIAMS supports research on a number of diseases disproportionately affecting women, including: osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint disorders (TMJ), fibromyalgia, and systemic lupus erythematosus (lupus). Lupus is a disease 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.

Osteoarthritis is the most common type of arthritis but researchers have been hampered by the fact that existing indices of the disease present a sometimes confusing and relatively insensitive index of disease onset and progression. Discovery of new and more sensitive biomarkers for onset and progression of osteoarthritis is a significant research need. To address these issues, the NIAMS has continued to develop the Osteoarthritis Initiative by expanding patient enrollment. Additionally, the NIAMS launched the Osteoarthritis Biomarkers Network, a program designed to hasten the pace of discovery of molecular biomarkers for osteoarthritis.

Researchers have made significant advances in developing treatment options for individuals with osteoporosis. NIAMS-supported researchers have recently evaluated the effectiveness of combining the bone-building treatment parathyroid hormone with alendronate, a drug that slows bone loss. Researchers discovered that combining these drugs produces no significant improvement in bone mineral density beyond that produced by the individual drugs. In addition, other NIAMS-supported researchers examining the effects of two bone active drugs in heart transplant recipients have found that both reduce the degree of bone loss commonly seen in the first year following transplant surgery. Other researchers have determined that elevated levels of homocysteine, an amino acid associated with increased risk of cardiovascular disease, may also be linked to the development of osteoporosis and related fractures. These findings provide additional insight in potential treatment and prevention options for osteoporosis.

Lupus is an autoimmune disease, and treatment often involves powerful drugs that will suppress the immune system. While these drugs may be able to keep the disease better controlled, in suppressing the immune system, they may leave the patient especially vulnerable to infection. Researchers supported by the NIAMS have found a potential treatment to suppress the abnormal, self-directed immune response that is responsible for lupus without hampering the body's ability to fight bacteria and viruses. Other researchers have also determined that people with lupus may develop fatty deposits in their arteries at an accelerated rate and show autoantibodies in their blood years before the symptoms of lupus appear.

National Institute of Biomedical Imaging and Bioengineering

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the research institutes within the NIH and was established by law in December 2000. The NIBIB received its first appropriation and grant funding authority in fiscal year FY 2002. As the NIBIB continues to grow

and structure programs, new initiatives are in development to support a variety of scientific areas, including programs aimed at fostering women's health research.

The NIBIB serves as the hub within the NIH for coordination of biomedical imaging and bioengineering efforts. The NIBIB: 1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; 2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; 3) formulates research goals and long-range plans with the guidance of the National Advisory Council on Biomedical Imaging and Bioengineering; and 4) sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

The NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FYs 2003 and 2004, the NIBIB funded grant awards that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women's diseases, such as breast cancer and disorders and conditions that predominate in women, including osteoporosis and temporomandibular joint diseases (TMJ). Researchers supported by the NIBIB plan to develop high resolution x-ray grids in mammography to detect breast cancer at its earliest stage, thereby greatly increasing patient survival rates. In addition, NIBIB-funded investigators are working on novel drug delivery treatments that will promote bone resorption for women suffering from osteoporosis.

During FYs 2003 and 2004, the NIBIB significantly increased support of women's health research in the following disease areas: aging, autoimmune disease, cervical cancer, contraception/reproduction, diabetes and diabetes research, epilepsy, HIV/AIDS, heart disease (education, research and coronary heart disease), lung cancer, stroke, stroke research, and temporomandibular joint disease (TMJ).

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The National Institute of Child Health and Human Development (NICHD) has a unique role to play in women's health research. Although the institute's mission is to ensure that babies are born wanted, timely, and healthy and that they develop to their full physical, emotional, and cognitive potentials, NICHD-sponsored research spans human growth and development. It starts from before conception and continues through infancy, childhood, and adolescence—all critical stages where the foundations for adult health and healthy women are established and are critically important. Given its mission, the NICHD research aims to overcome many of the complex challenges that face womens, in addition to their children and families.

For instance, NICHD-supported research is shedding light on how fibroids form, providing scientists with the preliminary knowledge that they need to begin developing non-surgical treatments for a condition that affects millions of women. In another study, NICHD scientists have found substances in blood that may predict preeclampsia in pregnant women, a complication that can be fatal. The full extent of this finding may be realized in future research leading to the development of treatments that can prevent or treat the condition before it becomes life-threatening, saving the lives of thousands of women.

Through the NICHD Maternal Fetal Medicine Units Network, researchers showed the remarkable effectiveness of a new progesterone treatment that reduces the risk of preterm birth in women who previously gave birth at less than 37 weeks. This is one of the first major discoveries in this area, despite extensive efforts over decades, and promises to help change obstetrical practice. Because of its far-reaching public health impact, the advance appeared in *Parade Magazine* (2004) as one of the year's leading medical advances and was featured on the front page of the *New York Times* (2003).

NICHD researchers also avidly pursue better outcomes to improve women's health around the globe. One of the most important

developments is a new treatment option for women in developing nations to protect their unborn infants from HIV. The inexpensive and simple drug-combination reduces the chance of mother-to-child transmission (MTCT) of HIV to less than 2 percent, similar to that of the more complex and expensive treatment in the developed world. Because of its promise to dramatically reduce MTCT rates, the Thailand Ministry of Public Health adopted this regimen as the standard for prevention of HIV MTCT, and the World Health Organization recommends this treatment as the first choice to prevent MTCT in women who do not need more complex therapies for her own health.

To share these scientific advances in women's health and other women's health information, the NICHD recently launched a new website, Women's Health Research at the NICHD. This new resource dedicated to women's health brings together a variety of information about women's health topics, and about ongoing research projects supported by the NICHD. In addition, it provides information about how to pursue research on women's health. The site also offers access to NICHD news releases, publications, conference and event schedules, and other information related to women's health (*www.nichd.nih.gov/about/womenhealth/women_health.cfm*).

The NICHD's advances in women's health are as wide-ranging as the institute's women's health portfolio. This includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are key to improving the quality of life for women.

National Institute of Dental and Craniofacial Research

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving craniofacial, oral, and dental health through research. As a central part of this mission, the NIDCR funds scientific research to prevent diseases and improve the quality of life for the millions of Americans who suffer from chronic diseases affecting the mouth and face. The NIDCR supports research in areas as diverse as understanding the oral infections that lead to dental decay, periodontal disease, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone disease; salivary gland dysfunction and disease; and connective tissue diseases and disorders. Because one quarter of all chronic pain is associated with the face and mouth, the NIDCR has become a leader in the field of pain research. The NIDCR's commitment to the fundamental study of the body's hard tissues—teeth, cartilage, and bone—has led to advances in biomaterials research and to the emerging field of tissue engineering and biomimetics—fields that use the body's own cellular and molecular processes to repair and regenerate tissues and organs. Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the NIDCR has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. Research advances that affect women, in particular, are to be found within many of the institute's broad research categories. This report highlights accomplishments and initiatives in the areas of chronic pain, temporomandibular disorders, osteoporosis and basic bone biology, cancers, autoimmune disease, human immunodeficiency virus (HIV) infection, health disparities, craniofacial anomalies and periodontal diseases, and systemic effects.

National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within the NIDDK's research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include: gestational diabetes; obesity (especially in racial and ethnic minority populations); coronary artery disease; cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome (IBS) and

other functional gastrointestinal disorders; osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis (IC); urinary tract infections (UTIs); urinary incontinence; and lupus nephritis (the kidney disease of systemic lupus erythrematosus). Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other Institutes and Centers (ICs), such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease. The NIDDK supports research that directly addresses the important women's health questions cited above, both through basic research directed to understanding underlying disease processes, and through clinical research that translates this understanding into therapies and preventive interventions. In FY 2003 and 2004, the institute has made progress in the following areas important to women's health, which are highlighted in this report: prevention and treatment of diabetes and its complications; osteoporosis; thyroid disease; irritable bowel syndrome and other functional gastrointestinal disorders; liver disease research; obesity and nutrition; kidney disease; urinary tract infections; urinary incontinence; and interstitial cystitis. The Office of Research on Women's Health has worked with the NIDDK to foster research in many of these areas.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Environmental agents likely play a role in a number of important female-predominant diseases. These include breast cancer, osteoporosis, ovarian dysfunction (e.g., premature menopause, polycystic ovarian syndrome, and ovarian cancer) uterine fibroids, and autoimmune diseases. The National Institute of Environmental Health Sciences' (NIEHS) approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds (both natural and synthetic) in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to determine the importance of the timing of exposure on disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases and environmental health regulators can better define standards that protect women from environmental triggers of these diseases.

Prevention and intervention efforts are major focuses of NIEHS activities. These efforts include hazard identification and characterization, both through traditional animal testing and epidemiologic studies and through incorporation of mechanistic considerations to arrive at new insights into the molecular basis of toxic effects. Although many people think of environmental exposures in terms of synthetic chemicals, the NIEHS also investigates natural compounds and the importance of diet and supplements in protecting health.

Identifying important triggers of disease is complicated by the fact that environmental exposures do not act in isolation. Underlying genetic susceptibilities, as well as the stage of life at which exposures occur, can have a profound effect on final disease risk. The NIEHS continues to investigate genetic susceptibilities to environmental disease risk and is spearheading the Environmental Genome Project that will help identify the important genetic variants of environmental response genes for both women and men. The importance of early exposures in later disease risk continues to be investigated both through individual laboratory studies and through the use of larger, life-time cohorts.

The NIEHS' Laboratory of Women's Health focused on important diseases in women, such as breast cancer, ovarian cancer, uterine leiomyoma, ovarian dysfunction, and pregnancy and parturition dysfunctions. The laboratory studied how these diseases develop and occur over the life span of a woman and how environmental toxins and stresses cause these diseases. The ultimate goal is to reduce the burden of environmentally related diseases. The laboratory initiated a clinical study, the Uterine Leiomyoma Longitudinal Intervention

Study, designed to define the growth dynamics of uterine leiomyomas through time and to develop markers for growing and/or clinically relevant leiomyomas which will be important in future studies of the etiology, therapy, and prevention of these tumors. The Laboratory of Women's Health also worked to develop genetically defined animal models that provide links between molecular medicine, human epidemiology, and experimental studies. These models provide opportunities to identify key genes and signaling mechanisms of the reproductive systems that interact with the environment over time at different stages of life. The overall goal is to integrate genetics, endocrinology, immunology, pathology, epidemiology, and clinical research to study diseases in women in order to discover new ways to prevent environmentally related diseases.

National Institute of General Medical Sciences

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training for the basic biomedical sciences. The NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. This knowledge is necessary in order to understand the disease process. Most studies supported by the NIGMS do not target any particular disease or condition, but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. Often basic research supported by the institute will result in findings pertinent to women's health.

The NIGMS supports research in drug discovery, synthetic chemistry and pharmacology, including studies in proteomics, glycomics, pharmacogenetics, and pharmacogenomics. These studies often have broad applicability to a wide variety of diseases or organ systems, including those specific to, or which disproportionately affect, women. For example, natural plant and animal products are a major source of bioactive agents. One such agent is taxol, which is derived from the bark of the yew tree. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. While very promising in the treatment of ovarian and breast cancer, only limited natural supplies of taxol were available. Improved approaches for isolation, purification, and synthesis have enabled wide-spread clinical trials of taxol. Unfortunately, taxol treatment, while effective, is often accompanied by severe side effects. Second-generation taxoids developed by NIGMS-supported investigator Dr. Iwao Ojima have distinct advantages over the parent drug in that they have outstanding oral bio-availability, have been found to be at least as active as the approved drugs when tested in human carcinoma cell lines and, most significantly, retain their activity against drug-resistant human carcinoma cells. Studies of second-generation taxoids continue to hold promise for improved efficacy with fewer side effects.

Inter-individual drug responses depend on genetic variation as well as modifying factors such as environment, diet, other medications, age, and gender. Under Program Announcement (PA) Mechanisms Underlying Individual Variations in Drug Response (PA-99-016), the NIGMS supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic/pharmacogenomic variations in drug metabolism and clearance. In addition, applications received in response to a Request for Applications (RFA) Pharmacogenetic Research Network and Database (RFA-GM-99-004), the NIGMS has built on this by supporting the formation of a coordinated Pharmacogenetic Research Network and Database. Dr. David Flockhart, M.D., Ph.D., director of the Division of Clinical Pharmacology at the Indiana University School of Medicine and a member of the NIGMS Pharmacogenetic Research Network, recently demonstrated that the effectiveness of tamoxifen therapy for the treatment and prevention of breast cancer may be limited by the use of drugs commonly prescribed to prevent the side effects associated with tamoxifen treatment. His study in the *Journal of the National Cancer Institute* (December, 2003) suggests that metabolism of tamoxifen may be modified by the genetic makeup of the

person taking the drug. In addition, he demonstrated that the antidepressants paroxetine and fluoxetine (normally prescribed to counter hot flashes, a side effect of tamoxifen therapy) inhibit the enzyme that breaks down tamoxifen into its most active metabolite, 4-hydroxytamoxifen. Genetic variations in metabolism of tamoxifen may account for differences in effectiveness of the therapy between patients.

The NIGMS extensively supports interdisciplinary research training of predoctoral and postdoctoral scientists, and the Medical Scientist Training Program (MSTP) provides training of students with both a medical and scientific background. These future scientists, with both M.D. and Ph.D. degrees, will be ideally poised to address research problems in cell biology, biochemistry, immunology, biophysics, molecular biology, and genetics, and to relate their results to clinical areas. The predoctoral training program in cell biology, molecular biology, and biochemistry encompasses research training on cellular mechanisms, enzymology, and molecular mechanisms relevant to understanding cell growth, activation, division, and motility. The genetics training program at the predoctoral level prepares future scientists to understand the genetic mechanisms operant in the inheritance of genetic factors, transcriptional control, mutagenesis, DNA structure, recombination and repair, and the role of genes in cell division and differentiation. Postdoctoral training programs in genetics foster the development of M.D.s and Ph.D.s with expertise in genetic approaches to disease. The training program in molecular biophysics focuses on the development of scientists able to determine the three-dimensional structures of biologically active molecules and the relationship of the structure to function. These future structural biologists will be in a position to rationally design drugs to treat diseases, such as breast cancer. The NIGMS training program, aimed at the chemistry/biology interface, has the goal of fostering more chemists with a knowledge and understanding of biological systems. This is an area that also will be critical for the design of new drugs and diagnostic and preventive approaches. This program complements the existing training program in the pharmacological sciences that prepares young scientists to investigate the biochemical systems that are amenable to pharmacological intervention and to investigate the pharmacology of drug action and drug toxicity.

A basic understanding of the etiology of a disease, the predisposing factors, the cellular processes involved, and the mechanisms that promote disease progression are necessary for prevention, early diagnosis and effective treatment of the disease. The NIGMS' support of fundamental research impacts on virtually all these areas. In addition, the NIGMS supports interdisciplinary research training at the predoctoral and postdoctoral levels, providing the personnel for biomedical research. Specific efforts on the part of the NIGMS in pharmacogenetics addressing inter-individual drug responses as they are influenced by genetic variation, as well as modifying factors, such as environment, diet, age, and gender, as well as other institute programs, can be found on the NIGMS homepage (*http://www.nigms.nih.gov*).

NATIONAL INSTITUTE OF MENTAL HEALTH

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders than boys. After puberty women have higher rates than men of depression, eating disorders, and anxiety disorders, including post-traumatic stress disorder. There are also differences in the course and severity of mental disorders between men and women. For example, men have an earlier average age of onset of schizophrenia, while women are more likely to suffer from the rapid-cycling form of bipolar disorder. Additionally, women are at increased risk of recurrence of depression during certain times of reproductive change, such as in the perinatal period.

The World Health Organization's study, The Global Burden of Disease, provided a measure of lost years of healthy life due to premature death, as well as years lived with disability. For the first time, the burden of

illnesses was shifted from an almost exclusive focus on premature mortality to one that included chronic illness. The study enabled a comparison of the burden of different illnesses. Based on 1990 data, depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder were among the top ten conditions accounting for years lived with disability in women. This public health burden stems from three aspects of the epidemiology of the disorders. First, these conditions are highly prevalent. For example, in a 1-year period, an estimated 12 percent of women meet criteria for depression and approximately the same percentage meet criteria for an anxiety disorder. Second, all four of the most disabling mental disorders have an early onset and a recurrent or chronic course. Third, since these disorders rise markedly in incidence in adolescence and peak in incidence in young to middle adulthood, they can adversely impact educational and occupational attainment, as well as social and interpersonal functioning. The study did not consider the impact of maternal mental illness on children in assessing disability burden, but in other numerous studies maternal mental illness has been associated with poorer child functioning. Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender differences in mental health and mental illness. Through crosscutting programs, such as the Women's Mental Health Research Team, the NIMH has fostered interdisciplinary collaboration and the translation of basic findings into applications to improve diagnosis, treatment, services, and prevention. This report highlights findings from areas of basic and clinical neuroscience, epidemiology and risk factors, and intervention development.

Research highlights in these areas are grouped by five major subheadings: 1) developmental aspects of sex and gender* differences; 2) mood and anxiety disorders; 3) eating disorders; 4) schizophrenia and other serious mental disorders; and 5) health behavior, AIDS, and mental health disparities. A section on Other Program Activities describes the Women's Mental Health Program and Team, and NIMH-sponsored meetings and research funding mechanisms relevant to women's mental health and sex and gender differences research.

National Institute of Neurological Disorders and Stroke

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease, a burden borne by every age group, by every segment of society, by people all over the world. Most nervous system disorders affect men and women equally, but certain disorders are more prevalent in, or are of special interest to, women. Major examples include multiple sclerosis, pain, stroke, and epilepsy. The NINDS supports basic, translational, and clinical research on these and other neurological disorders.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that causes inflammation, demyelination, and damage to nerve fibers. MS is one of the most common neurological disorders leading to disability in young adults. The disorder is usually characterized by attacks of muscle weakness; coordination, balance or vision problems; abnormal sensations; and sometimes cognitive impairments. Hormonal factors may influence MS; some forms of MS are twofold more frequent in women and fewer relapses are reported during pregnancy. NINDS-sponsored research is underway to compare the efficacy of standard therapies alone and in combination (CombiRx trial), to develop methods to protect against damage to myelin and nerve fibers, to identify MS biomarkers, and to better understand the genetic, hormonal, and environmental contributions to the disease.

* A 2001 report from the Institute of Medicine, Exploring the Biological Contributions to Human Health: Does Sex Matter?, recommended greater precision in terminology used to reference findings from studies comparing health outcomes in males and females. Accordingly, in the present report, the term "sex difference" is used to refer to biological variables, and the term "gender difference" is used to encompass psychosocial, behavioral, and cultural variables.

Chronic pain results from pain signals that keep firing in the nervous system for weeks, months, or even years. Some chronic pain conditions, like migraine headaches or fibromyalgia, tend to be diagnosed more often in women than in men. Treatments for chronic pain can include medication, acupuncture or relaxation techniques, local electrical stimulation or brain stimulation, psychotherapy or behavior modification therapies, or surgery. The NINDS research portfolio contains a broad range of projects focused on understanding pain pathways and mechanisms of pain processing, modulation and regulation, and pain management. Specific topics include research about the peripheral, spinal, brainstem, and cortical mechanisms and pathways of pain; about neuropeptide, cholinergic, and glutamate systems involvement in pain; about the mechanisms of anesthesia and analgesia; and about central and post-stroke pain, migraine, neuropathic pain, visceral pain, pelvic pain, painful peripheral neuropathies, including diabetic and HIV-associated neuropathies, back pain, muscle pain, cancer pain, and inflammatory pain.

Strokes are caused by a rapid disruption in the blood supply to part of the brain as a result of blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or a sudden severe headache. Stroke is the third leading cause of death in the United States, and a major cause of disability in both women and men. Although women, in general, have a lower risk of stroke than men, because of their longer life expectancy they account for 60 percent of stroke fatalities. The NINDS stroke research program ranges from basic investigation of stroke mechanisms through large studies of risk factors and clinical trials aimed at prevention and treatment. Interventions under investigation include drugs, surgery, vitamins, physical therapy, and psychosocial modalities. Research is also targeted to special issues of stroke in various populations, including women. For example, an NINDS-sponsored prospective cohort study is examining the risk of stroke in patients with systemic lupus erythematosus (SLE), an autoimmune disease that predominantly strikes women.

Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. While anti-epileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for some the seizures are resistant to therapy or the treatments cause unacceptable side effects. Women with epilepsy can face special problems, such as increased seizure frequency during phases of the menstrual cycle (called catemenial epilepsy). Female patients taking selected AEDs must consider changing medications if they wish to become pregnant, since certain AEDs can cause higher-than-normal rates of birth defects. In addition to many basic and translational studies of epilepsy and epileptogenesis, the NINDS also supports clinical research in epilepsy. Several of these clinical projects are targeted to issues of special interest to women, such as hormonal influences on seizures and neurodevelopmental effects of *in utero* exposure to AED therapy.

NATIONAL INSTITUTE OF NURSING RESEARCH

The National Institute of Nursing Research (NINR) supports clinical and basic research to establish a scientific basis for the care of individuals across the life span. The research mission of the NINR is available at *http://www.nih.gov/ninr/research/diversity/mission.html*

The focus of women's health studies has often centered on reproductive function. However, emerging models of health care services need to address all circumstances of women's health across the lifespan. Nursing has a long tradition of concern for the health of women and of developing and providing services oriented to the needs of women. Investigators and nurse scientists supported by the NINR have contributed new knowledge addressing women's health related to cardiovascular health, midlife and menopause, aging, cultural and ethnic variations, HIV/AIDS, cancer, chronic disease, women as caregivers, and other related issues.

In addition, the NINR also continues a strong program of research into women's reproductive health. NINR-funded researchers have explored many aspects of care during pregnancy and childbirth through studies that focus on care during pregnancy and delivery, maternal issues in infant care and child development, and adolescent sexuality and pregnancy.

These results help to give nurses and other health care workers greater understanding of the wide range of women's health issues.

A number of NINR-funded studies are examining the cardiovascular health of women, which leads to over 250,000 deaths a year among women. Studies have identified different early and acute symptoms of heart attack between women and men, and factors unique to women's recovery. To decrease the number of cardiovascular disease-related deaths, nursing care of women needs greater emphasis on awareness, heart-healthy habits, and preventive measures.

Menopause is an important phase in a woman's life. The Ohio Midlife Women's Study, involving both pre- and postmenopausal women, found that roughly one-third of women respondents showed signs of anxiety, and one-quarter suffered from depression. In another study, Black women tended to note menopause as a normal phase of life, while white women focused more on the signs of aging. Older Latina women identified menopause as a normal adult phase that women must pass through, and is often a time for women to focus on personal needs and reorder the harmony and balance in their life.

Loss of bone mineral density accelerates in women after menopause, increasing the risk of osteoporosis-related fracture. Studies have focused on exercise interventions, and on racial differences in body mass and bone density. For older women with the APOE-4 genotype, a low-fat diet may improve cholesterol levels, but it may worsen certain risks for other women.

Regular exercise is an important goal of the Healthy People 2010 initiative, but more than one-quarter of women in the United States report minimal leisure-time physical activity, and among women activity levels are lower for Blacks than for whites. Several studies have targeted programs to help boost exercise levels, especially for older women.

Other studies have examined symptom management and quality of life for HIV-positive women related to sleep, emotional distress, sexuality, stigma, and family function.

Recent studies on breast cancer have improved the assessment of lymphedema and examined nursing case management with older breast cancer patients. Studies in chronic illness have focused on identifying symptoms of and targeting interventions for irritable bowel syndrome, fibromyalgia, rheumatoid arthritis, and multiple sclerosis. The Women to Women (WTW) intervention, a computer-based health care intervention, provided self care and treatment information for rural-dwelling women living with a variety of chronic conditions.

Family caregivers, who frequently are older and female, often neglect their own health care, and several studies have addressed the stresses of caregiving, which may affect women more than men.

Studies of women in pregnancy and childbearing have identified risk factors for preeclampsia, protective factors for Latina women, caregiving for young children with diabetes, and pregnancy and HIV prevention programs for low-income and minority adolescents. In addition, other studies have examined the responses of couples to a miscarriage or to the loss of a baby in infancy.

The NINR continues to develop and implement initiatives related to its "strategic plan on reducing health disparities." The three components of the NINR's strategic plan on health disparities include research, infrastructure development, and outreach. Identifying Effective Strategies to Reduce Health Disparities is one of five NINR Research Themes for the Future identified in 2003. The Research Themes document is available at *http://ninr.nih.gov/ninr/research/themes.do*

National Institute on Aging

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other

dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2003 and 2004, NIA-supported researchers made important progress in a number of women's health-related areas, including:

- Investigators have reported new findings regarding the risks and benefits of hormone therapy with regard to cognition, identified a potential link between diabetes and cognitive decline in postmenopausal women, and continued to seek ways to reduce the burden on caregivers of chronically ill patients.

- *Osteoporosis*. Investigators have uncovered a new cellular pathway for estrogen action on bone, and have elucidated the effects of a hormone that inhibits bone turnover and net loss of bone. These basic findings may have future clinical implications.

- *Reproductive Health/Menopause*. In 2004, NIA-supported researchers made the surprising discovery that contrary to accepted scientific dogma, oocyte (egg) production continues well into old age — in mice, at least. Other NIA-supported researchers have developed a new rodent model of menopause, uncovered a possible new mechanism for hot flashes, and made important findings regarding depression and the menopausal transition.

The NIA has several ongoing research initiatives dealing specifically with women's health. These include: 1) the Study of Women's Health Across the Nation (SWAN). The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in women of various racial/ethnic backgrounds; and 2) the Women's Health Initiative Study of Cognitive Aging (WHISCA), an ancillary project of the Women's Health Initiative Memory Study and the Women's Health Initiative (WHI), a randomized clinical trial of hormonal therapy. Since 1999, WHISCA has investigated the effects of hormonal therapy on longitudinal changes in memory and specific cognitive functions in older non-demented WHI participants.

The NIA supported several workshops on women's health-related topics in 2003 and 2004. In addition, the NIA is currently supporting an extensive program of research pertaining to health disparities among special populations; much of this research is relevant to the health concerns of minority women.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports research on the behavioral and medical causes and consequences of alcohol use, abuse, and alcoholism, and on new ways to prevent and treat these significant public health problems. The primary beneficiaries of this research include not only those directly affected by alcohol abuse but society as a whole. It is estimated that the costs per year top $185 billion and cause greater than 100,000 deaths per year.

There are estimated to be 14 million alcohol-abusing or alcohol-dependent individuals in the United States, of which over 4 million are women. Women drink less alcohol and have fewer alcohol-related problems and dependence symptoms than men, but among the heaviest drinkers women equal or surpass men in the problems that occur because of their drinking. In contrast to young people who begin drinking at age 21, equal numbers of young men and women who begin drinking at age 13 are four times more likely to develop alcohol dependence sometime during their lifetime.

The NIAAA continues to expand its research portfolio on the impact of alcohol and alcohol misuse on women. Collaboration with other federal agencies remains an important priority within this area of research, and has yielded important scientific advances in our understanding of the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women. In fiscal years 2003 and 2004, research on women and alcohol was addressed by six central themes: 1) psychosocial determinants

of drinking in women; 2) violence and other social consequences of alcohol misuse; 3) impact of alcohol use and misuse on women's physiology; 4) drinking during pregnancy; 5) treatment of women with alcohol use disorders; and 6) biobehavioral correlates of alcohol use and misuse in women.

Regarding psychosocial determinants of alcohol misuse in women, a study of rural women in the United States, found that victimization is a risk factor for alcohol and other drug disorders and that women experience greater stress and have fewer resources to deal with these problems. A study of college students has shown that although lesbian and heterosexual women did not differ in their alcohol consumption, sexual identity is an important predictor of alcohol and other drug abuse (AOD). Lesbian women had a greater likelihood of experiencing AOD, including smoking of cigarettes and marijuana, and use of ecstasy and other drugs. In a large epidemiological study, a 1.8 percent lifetime rate of DSM-III-R alcohol dependence was found for women born before 1940, as compared to a rate of 13 percent for women born after 1960 (men: 15 percent and 28 percent, respectively). A longitudinal analysis of the long-term antecedents of suicidal ideation among women in the United States revealed that such ideation is predictable from prior suicidal ideation, hazardous drinking, adverse childhood experiences, and domestic stressors. A comparison of high-risk women in South Africa and among U.S. Plains Indians indicates that damage from fetal alcohol syndrome (FAS) is less detectable in the U.S. Plains Indians, although both groups report high levels of binge drinking. It is surmised that body mass index and lifelong and current nutrition may have an important impact on the relative risk of an FAS birth. Chronic alcohol abuse alters immune defenses and increases infections in adults. A study was done to see if women who drank during pregnancy increased the risk of sepsis in very low birthweight premature newborns. Early onset sepsis was 15-fold higher in the alcohol exposed group, compared to the findings for the matched control group. Early onset sepsis in the alcohol plus cocaine exposed group did not differ from findings in the control group. Gender analyses from Project MATCH found a more rapid rate of progression of alcoholism (i.e., more rapid course of and appearance of alcohol dependence symptoms) among women, compared to men. In addition, there was a much higher prevalence of physical, emotional, and sexual abuse among females in the treatment-seeking population than among men, consist with other studies. An ongoing randomized clinical trial is focusing on reducing HIV risk behaviors among women seeking help for alcohol problems. The study will evaluate the relative effectiveness of combined behavioral intervention (CBI), a state-of-the-art, empirically based treatment for addressing alcohol problems in dependent drinkers, followed by a HIV-risk reduction intervention (HIV-RR) and CBI followed by an intervention limited to dissemination of HIV information (HIV-I). Researchers believe women who respond positively to alcohol treatment and who receive HIV-RR will do better than their counter parts in HIV-I. Another ongoing study is using a community reinforcement approach and enhanced job training for women. Previous research indicates that alcoholism is the most common health problem among homeless women, and since women and families now comprise about 30 percent of the homeless population, it is important to find feasible approaches to keep these women in treatment. This trial is evaluating the relative effectiveness of three approaches to treatment, including case management (CM), the community reinforcement approach (CRA), and an enhanced CRA called Community Reinforcement, Employment, and Training Enhancement (CREATE), in reducing drinking and improving employment status and housing stability among homeless women with alcohol use disorders. It was found that the CRA was more effective than CM, but many women relapsed when treatment ended and their abstinence-contingent, free housing ended. The current project includes an enhanced CRA which provides aftercare, job training, and employment-oriented motivational interventions during the high-risk, post-treatment program. Homeless women with alcohol use disorders are among the most difficult groups

to engage and retain in treatment so positive results from this study could have important public health implications. The mechanisms underlying gender differences in alcohol drinking behavior and alcohol's effects are poorly understood. Alcohol significantly and consistently decreases whole brain metabolism of glucose. The magnitude of the changes seen was greater in males than in females. This study showed a markedly blunted sensitivity to the affects of acute alcohol on brain glucose metabolism in women that may reflect gender differences in the alcohol's modulation of GABAergic neurotransmission.

Fiscal years 2003 and 2004 were years of continued scientific research on gender-based differences in the causes, consequences, prevention, and treatment of alcohol use disorders. Research in the area of genetics is consistently revealing differences at the molecular level that helps to explain gender differences in the rates of alcohol dependence and other psychiatric disorders. Clinicians may soon be able to unravel the problems and identify and intervene with those at increased risk for alcohol use disorders before problems with alcohol begin. Studies evaluating approaches to preventing fetal alcohol spectrum disorders have shown an acceptance of alcohol screening and brief interventions among women attending obstetric clinics. There may be a decrease in violence that may be attributed to brief interventions. New strategies and collaborations among different disciplines will lead to research and clinical study results that will inform our efforts to improve the quality of life of women affected by the misuse of alcohol.

NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms, as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD also conducts and supports research and research training that are related to disease prevention and health promotion.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The institute supports efforts to create devices that substitute for lost and impaired sensory and communication functions. A number of diseases, disorders, or conditions within the mission of the NIDCD affect women disproportionately. Examples of significant research programs have been selected for inclusion in this report. Highlights of the latest research advances and plans for the future in these areas appear later in this publication.

NATIONAL INSTITUTE ON DRUG ABUSE

The National Institute on Drug Abuse (NIDA) supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. The NIDA-supported science addresses the most fundamental and essential questions about drug abuse, ranging from the molecule to managed care, and from DNA to community outreach research. Within this science, there is a major NIDA effort to investigate issues specific to women and to study sex/gender differences. Leadership for this effort is provided by NIDA's Women & Gender Research Coordinator and Deputy Coordinator along with NIDA's Women & Gender Research Group, which has representation from all of NIDA's program branches, offices, and centers. The major goal of this effort is to infuse the study of sex/gender differences and issues specific to females in all areas of drug abuse research and to disseminate research findings in this area.

Over the past decade, the NIDA has engaged in a variety of initiatives to promote research on women and sex/gender differences and the drug abuse research field has responded as evidenced by a growing number of NIDA-supported research grants and publications in this area.

Today, the NIDA supports sex/gender-based research in all of its major program areas. From basic research on the biological underpinnings and consequences of drug abuse to field research on etiology and consequences of drug abuse, to research on prevention and treatment, evidence for the importance and fruitfulness of taking a sex/gender-based research approach and analyzing data separately for males and females is growing. NIDA-supported research is repeatedly showing that sex/gender matters in drug abuse.

The research findings published over the past 2 years are representative of NIDA's research on women and gender differences. These research findings fall into six major research areas: 1) biological mechanisms and consequences, 2) prenatal exposure to drugs, 3) nicotine addiction, 4) adolescents, 5) treatment and treatment services, and 6) HIV/AIDS. These findings strongly suggest that the identification and understanding of sex/gender differences can improve our understanding of the nature, etiology, and consequences of drug abuse and that it may have implications for tailoring prevention and treatment interventions to maximize outcomes for both males and females.

Reports of the Institutes and Centers

FOGARTY INTERNATIONAL CENTER

The Fogarty International Center (FIC) supports a range of research and research training programs, many of which include activities on women's health. Research training programs working in low- and mid-income nations on topics such as population and health, maternal and child health, AIDS, and stigma and global health represent FIC's efforts that include significant attention to women's health issues. The ORWH supports many of these efforts, along with lead NIH Institutes, including the NICHD, the NIAID, and the NIA. The FIC and the ORWH have teamed up additionally to explore issues facing women in science in developing countries and to consider gender and global health issues. These initiatives have informed the FIC and other Institute's and Center's (IC's) programmatic directions.

Accomplishments

The Fogarty International Center, the international component of the NIH, addresses global health challenges through innovative and collaborative research and training programs and supports and advances the NIH mission through international partnerships.

The FIC's research and research training programs address a wide range of topics of concern to the global health community, including infectious diseases, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, population dynamics, environmental and occupational health, bioethics, trauma and injury, tobacco control, and biodiversity.

Many of FIC's research training programs include activities aimed at improving women's health. In particular, the FIC International Research and Training Program in Population and Health supports research training in reproductive processes; contraceptive development; and demographic studies of population health issues, including rapid societal changes, societies under stress, and aging. The FIC International Maternal and Child Health Research and Training Program supports research training to address the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The FIC AIDS International Training and Research Program funds training for research to address issues of HIV infection, many of which have particular relevance for women: stigma associated with HIV/AIDS, perinatal transmission of HIV, HIV transmission through breast feeding, and female-controlled methods to reduce sexual transmission of HIV (microbicides, biomedical interventions, and behavioral interventions). The Fogarty International Research Collaboration Award (FIRCA), a small grants program that fosters international research partnerships between NIH-supported U.S. scientists and their collaborators in the developing world, provides the opportunity for a wide spectrum of research on women's health problems and issues. Some examples of areas of research supported by the FIRCA program that include women are obesity, smoking cessation, and cervical and breast cancer.

In FY 2002, the FIC launched the Stigma and Global Health Research Program in partnership with several other NIH ICs and with the ORWH. The first awards under this program were made in FY 2003, and address the role of stigma in health, and on how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups, and societies worldwide. Research projects supported by this program study how stigma associated with specific health conditions interacts with individual or group characteristics (such as gender, race, religion, sexual orientation, and nationality). Some projects are specifically focused on linkages between gender, stigma, and health, including AIDS stigma and gender discrimination in urban

Indian health care systems; culture, gender, and health care stigma in Parkinson's disease in Taiwan; and stigma, gender, and risk behaviors in school youth.

The Effects of Supplementation with Multivitamins and Vitamin A on Prevention of Mother-to-Child HIV Transmission

The need to better understand the role of nutrition and micronutrients in HIV transmission and pregnancy outcomes among HIV-infected mothers is essential. Scientific research continues to identify less expensive and easier interventions that prevent HIV infection from mother to baby. Tanzanian researchers have found that supplementation with multivitamins (Vitamin B, C, and E) without vitamin A had no effect on HIV transmission from mother to the baby up to 6 weeks after birth. This vitamin combination did, however, reduce the risk of low birthweight, fetal death, and severe prematurity. Surprisingly, Vitamin A supplementation appeared to increase the risk of HIV transmission during the same time period. A related study from Malawi found that vitamin A supplementation to HIV-positive pregnant women reduced both anemia and increased birthweight among their offspring. In both these studies the rate of HIV transmission at 6 weeks and 24 months of age was the same. The formulation and dose of vitamin A differed between the studies in Malawi and Tanzania, which may explain the differences in the results. Supplementation with vitamins B, C, and E seems to have some benefit to improve birth outcomes among HIV-infected women, but does not seem to affect the risk of HIV transmission, except for possibly women with advanced disease. While further research is clearly warranted, the finding that vitamin A supplementation appears to increase the risk of HIV transmission, even during breast feeding, discourages further research on this vitamin as a possible intervention for the prevention of HIV transmission.

Gender Differences in Perinatal Acquisition among African Infants

Differences in HIV transmission between men and women can be attributed to many factors, some of which are anatomical and physiological and some of which are behavioral. A few studies have found higher rates of HIV transmission from mother to girl infants than boy infants, but these studies have not been able to identify if the female babies were at increased risk of transmission during pregnancy, during labor and delivery, or during breast feeding. Researchers at the Johns Hopkins University and the University of Malawi examined the rates of HIV transmission among girls and boy infants at birth and at 6 to 8 weeks post-delivery. Infants were enrolled in two studies to evaluate two different infant drug regimens to prevent HIV transmission. At birth, the infant girls were twice as likely than the boys to be HIV infected, indicating that the risk of infection was higher for girls during pregnancy. At 6 to 8 weeks of age, among those infants not infected at birth, the increased risk for girls continued but it was not as strong, indicating that the risk of transmission through breast feeding might be increased for girls too. After the researchers adjusted for the drug regimens used in the studies and other factors that might influence HIV transmission, the increased risk among infant girls still remained. Two explanations are possible. One is that infant girls are more susceptible to HIV infection before birth, due to yet to be determined genetic, immunologic, hormonal, or environmental factors. The second is that male and female infants are equally susceptible, but more infected boys are likely to die before birth than girls so the transmission among infant girls appears to be higher. These finding highlight the need for sex and gender analyses in many research studies, even when differences are not expected, if we are to better understand diseases and health conditions.

Substance Abuse and Sexual Abuse among South African Adolescents

Sexual assault and rape among adolescents is a serious and growing concern in the United States and abroad. The World Report on Violence and Health from the World Health Organization (2002) concluded that such attacks constitute a serious global health problem. Supported by the FIC International Tobacco and Health Research and Capacity Building Program, researchers from Pennsylvania State University and Tufts University,

working in South Africa with colleagues from the University of Cape Town, studied 939 students randomly selected from 2,946 total questionnaires in grades 8 and 11. The authors found than between 3 and 12 percent of students reported attempted rape, and an additional 5 to 7 percent reported actual rape. Significantly, girls were more likely to be victims of attempted rape than boys, but the both boys and girls were equally likely to be victims of actual rape. There was a clear increase in attempted and actual rapes of children in one parent or one parent plus stepparent households. Drug and alcohol use by the child was also correlated with childhood rape. In addition, suicide attempts, as well as suicidal thoughts and dialogue, were highly correlated with sexual abuse. Sexual abuse of children is a serious and growing global concern. This paper helps to identify some of the correlates, such as suicide ideation and attempts, and alcohol and drug abuse. In light of these findings, the effective prevention of sexual abuse and rape of adolescents in South Africa (and perhaps in other geographic areas) would benefit from a multifaceted approach, including a focus on substance abuse and the psychological health of minors.

National Wealth and Individual Socioeconomic Status As Predictors of Women's Obesity in the Developing World

As the global epidemic of obesity worsens dramatically in the developing world, it is vital to understand how social and economic factors affect the prevalence of obesity. Through the FIC International Training Program in Population Health, researchers from the University of North Carolina–Chapel Hill used recent health and education data from national surveys conducted in 37 developing countries to identify the level of economic development where women's obesity begins to influence inequities in health. The data was collected between 1992 and 2000 in countries in Sub-Saharan Africa, Latin America and the Caribbean, Asia, North Africa, and the Middle East. Researchers ran multilevel logistic models on the risk of being obese given a women's age, socioeconomic status (SES), and a country's gross national production (GNP) per capita. In general, the researchers found that obesity is more prevalent in countries with higher levels of GNP per capita. Within low-income countries, obesity was much more likely among higher SES women, while in the upper-middle-income countries the risk of obesity was higher among women with lower SES. In lower-middle-income countries, the pattern between SES and obesity was mixed. These findings should encourage policymakers to develop obesity interventions that are appropriately targeted to high-risk groups, and designed according to local conditions. The research also highlights that as countries undergo economic growth, obesity is likely to increase as a public health problem in the absence of effective interventions and policies.

Birth Outcomes in High Altitude Settings

The 140 million persons living at high altitude worldwide comprise the single largest group at risk for low birthweight. Next to preterm delivery, IUGR poses the greatest risk to neonatal or infant survival. Partly as a result, Bolivia, the highest country in the western hemisphere, also has the highest infant mortality. While lack of health care and poor nutrition play important roles, altitude is also a likely contributor, given that neonatal and infant mortality increase in proportion to the rise in altitude-associated IUGR. Supported by a Fogarty International Research Collaboration Award, a team of U.S. and Bolivian researchers set out to study altitude-associated IUGR and preeclampsia in women of high (Andean)- vs. low (European)-altitude ancestry living in Bolivia. They obtained birth records for 3,500 births in Bolivia at low, medium, and high altitudes and found that altitude-associated IUGR was three times greater in the European than Andean group. In addition, hypertension and fetal and neonatal complications were also more common at high altitudes. Stillbirths were three times more common in the preeclamptic women at high vs. low altitudes—a finding of considerable public health significance. The studies demonstrated that chronic hypoxia and preeclampsia act additively to reduce birth weight and interactively to raise intrauterine mortality. This research highlights the increased health

risks for pregnant women and their babies living at high altitudes and the need for research and interventions that specifically target these populations.

Initiatives

Program Announcements (PAs)

- **AIDS International Training and Research Program (AITRP)**
  This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries to conduct multidisciplinary biomedical and behavioral research capacity to address the AIDS epidemic in the collaborating country. The program supports research on women's health in the general areas of mother-to-child transmission and sex/gender-related science and issues. The ORWH contributes to this initiative.

- **Fogarty International Research Collaboration Award (FIRCA)**
  This program provides funds to foster international research partnerships between NIH-supported U.S. scientists and their collaborators in countries of the developing world. The FIRCA program aims to benefit the research interests of both U.S. and foreign collaborators while increasing research capacity at the foreign site. Some examples of research supported by the FIRCA program that focus on women's health include: obesity in women, cervical cancer, breast cancer, and smoking cessation in women.

Request for Applications (RFAs)

- **Global Health Research Initiative Program for New Foreign Investigators (GRIP)**
  The Global Health Research Initiative Program for New Foreign Investigators (GRIP) is intended to promote productive re-entry of NIH-trained foreign investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries. Examples of topics related to women's health under this initiative include: HIV/AIDS prevention in Chilean women, mitotic checkpoint and genomic stability in ovarian cancer, interventions to reduce HIV[1] after delivery, and tumor progression and apoptosis in mouse mamillary gland. The ORWH contributes to this initiative.

Conferences and Workshops

- **Colloquia on Career Path Issues and Gender/Global Health**
  The FIC, working closely with the ORWH and the NIEHS, convened a 2-day consultation in October 2003 of scientists from the United States and developing countries to consider career path challenges facing women in science in resource-poor countries. Best practices that assist women's career development in these countries were identified and recommendations for action were made, including the need to support skill-building workshops for women scientists in the developing world that would better enable them to take on leadership roles within health research and/or policy settings in their home countries.

- **Forum on Exploring the Potential Collaborations for Sex and Gender and Global Health Research**
  The FIC, the ORWH, and the Canadian Institutes of Health Research and its Institute on Gender and Health organized this forum in April 2004. Representatives from several international research funding agencies, as well as 18 components of the NIH, discussed existing programs focused on gender and global health research, as well as potential future partnerships or joint efforts in this area and identified potential areas of common activity. These are now under consideration.

Plans for Future Activities

Following up on a recommendation from the October 2003 career path workshop (see above), the FIC will sponsor a training session for women health scientists with a focus on professional development and gaining leadership skills in FY 2005. The 2-day training session will recruit participants from Fogarty's Global Health Research Initiative Program for

New Foreign Investigators. Participants will be offered sessions on basic leadership and career-building skills, and will also engage in sessions highlighting their career needs, the current climate for women in their home institutions, existing programs supporting women scientists in their country or region, and obstacles to their career growth. The latter sessions are intended to garner suggestions for a more extensive leadership program in the future.

NATIONAL CANCER INSTITUTE

This report describes many of the activities and accomplishments of the National Cancer Institute's (NCI's) research programs in fiscal years 2003 and 2004, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, and lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

Cancer continues to take a devastating toll on American women. In 2005, an estimated 662,870 women will have been diagnosed with cancer, and approximately 275,000 women will have died of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. In the 1990s, cancer incidence rates for all cancers combined decreased for men and remained relatively stable for women. Cancer incidence rates for women have since declined slightly, from 1999 to 2001. Mortality rates have decreased for all cancers combined in the general population and for eight of the top 15 cancers in women. Lung cancer death rates among women leveled off for the first time between 1995 and 2001, after increasing for many decades. Comparison of 5-year survival rates for cancer patients diagnosed in the years 1975 to 1979 to those diagnosed from 1995 to 2000 show improvement overall, although less significantly for women than for men.

The NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported at the NCI and through research grants, a number of specific programs and activities in the NCI focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group clinical trials cooperative group in the Division of Cancer Treatment and Diagnosis, and the Breast and Gynecologic Malignancies Faculty and the HPV Working Group in the Center for Cancer Research.

The NCI supports a number of broad-based research programs that apply to all types of cancer in both women and men. Through its strategic planning process, the NCI has identified many of the questions that need to be answered, areas of research and care that need to be supported, and infrastructure that needs to be strengthened to ultimately eliminate the suffering and death due to cancer. Seven strategic priority areas for investment are outlined in The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2006 (*http://plan.cancer.gov/*). As part of the planning process, the NCI periodically examines their progress in meeting strategic goals, and has recently released a report that assesses progress in addressing research priorities identified in the 1998 report of the Breast Cancer Progress Review Group (PRG). This report, as well as other PRG reports, implementation plans, and additional information is accessible from *http://planning.cancer.gov/disease/index.shtml*.

NCI staff participate in multiple, diverse scientific partnerships and collaborative activities with other federal and nonfederal scientists. By working with partners from public, private, and academic settings, and focusing investment in strategic areas with high potential, we take advantage of opportunities to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application.

Accomplishments

Trends In Cancer

Accurate information on the incidence and impact of disease is critical to decisionmaking

in science and public health. For this reason, the NCI has established a number of programs and initiatives to provide surveillance infrastructure, track trends, and report cancer statistics. The NCI continues to expand its surveillance efforts to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country.

Cancer Biology and Genetics

Basic studies exploring the science of how cancer develops and progresses form the foundation of cancer research. Identifying, at the molecular and cellular level, the fundamental processes that underlie a cell's normal development and transformation from normal to premalignant to malignant can lead to new prevention, detection, diagnosis, and treatment approaches. The NCI supports initiatives and programs that stimulate interdisciplinary research on cancer biology and genetics.

Preclinical Research

The NCI supports a broad range of pre-clinical research initiatives and resources to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer.

Clinical Research

The NCI's clinical trials system includes researchers from NCI's intramural program, Cancer Centers, Cooperative Groups, Specialized Programs of Research Excellence (SPOREs), Community Clinical Oncology Program (CCOP), minority-based CCOPs, and investigator-initiated grants. These scientists conduct over 1,500 clinical trials annually to evaluate improved and novel cancer prevention, early detection, diagnosis, treatment, and quality-of-life strategies.

Cancer Control and Outcomes

The NCI supports patient-oriented research that includes intervention, nutrition, chemoprevention, biobehavioral influences on disease, cancer screening, pain and symptom management, quality of life, ethics, confidentiality, and understanding health disparities. For example, the NCI plans to establish Centers for Transdisciplinary Research on Energetics and Cancer (TREC: *http://cancercontrol.cancer.gov/TREC/*), modeled after the successful Transdisciplinary Tobacco Use Research Centers (TTURCs), to foster transdisciplinary collaborations that aim to reduce the cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.

Advanced Technologies

The NCI supports the development of highly effective advanced technologies and their use to streamline research, enhance the options for patient care, and connect investigators with one another and with the heath care provider and patient communities.

Addressing Health Disparities

The NCI supports a number of programs to understand the causes and extent of cancer health disparities and to develop and implement culturally appropriate and sensitive interventions for the elimination of such disparities. Research studies have provided definitive evidence that equal treatment at the same stage of disease yields equal outcomes across all populations. A dramatic reduction in cancer incidence, as well as mortality, could be achieved by equitably applying evidence-based interventions for tobacco control and energy balance; providing equal access to clinical trials; and providing universal access and encouraging utilization of available, state-of-the-science interventions for cancer prevention, early detection, and treatment with follow-up care.

The NCI's Center to Reduce Cancer Health Disparities (*http://crchd.nci.nih.gov/*) provides the organizational locus for the critical tasks needed to translate discovery research into delivery of health disparity interventions. The Trans-HHS (Health and Human Services) Cancer Health Disparities Progress Review Group met in 2003 to identify new opportunities for HHS agencies to address cancer health disparities, implement new initiatives to eliminate them, and evaluate progress toward that end. Their report, released in March 2004, can be viewed at *http://www.hhs.gov/chdprg/pdf/chdprg.pdf*.

Cancer Information and Education

The NCI educates cancer patients, health and research professionals, and the public about women's health in a variety of formats. The NCI *Cancer Information Service (CIS)* shares information about cancer prevention, risk factors, symptoms, diagnosis, treatment, research, and quitting smoking. CIS information specialists provide the latest, most accurate information about cancer by telephone (1-800-4-CANCER), TTY (1-800-332-8612), and on the Internet through LiveHelp instant messaging service on NCI's website (*http://cancer.gov*). The CIS also provides printed and electronic NCI publications through the NCI Pubs Locator (*https://cissecure.nci.nih.gov/ncipubs/*) or by calling 1-800-4-CANCER. Through its Partnership Program, the CIS works with established national, regional, and state partner organizations to reach and educate minority and medically underserved women with limited access to health and cancer information.

The NCI also provides information to the public, the cancer community, and journalists through its website, *http://www.cancer.gov*. Included are press releases and fact sheets (*http://www.cancer.gov/newscenter*), supplemented with in-depth background information through NCI BenchMarks (*http://www.cancer.gov/newscenter/benchmarks*), NCI Clinical Trial Results (*http://cancer.gov/clinicaltrials/results/*), the NCI Cancer Bulletin (*http://cancer.gov/ncicancerbulletin/cancerbulletin*), the biannual Cancer Progress Report (*http://progressreport.cancer.gov*), and the annual publication of
The Nation's Progress in Cancer Research (*http://planning.cancer.gov/planning/budget.shtml*). The NCI's Women's Health Page provides information about initiatives, reports, and meetings pertaining to women's health issues (*http://planning.cancer.gov/whealth/*). Cancer information is also provided through staffed NCI exhibits at key conferences, meetings, and events.

The NCI's Office of Education and Special Initiatives (OESI; *http://www.cancer.gov/aboutnci/oesi*) has developed the Clinical Trials Education Series, a group of print and audiovisual materials, and a web-based course about participating in cancer clinical trials. The OESI also sponsors breast and cervical cancer screening education programs that target health professionals. The OESI Facing Forward Survivor Series, which includes Spanish language adaptations, addresses the issues that survivors face after treatment.

Breast Cancer

Although advances in prevention, detection, diagnosis, and treatment are having a beneficial impact on breast cancer incidence, mortality, and survival, this disease continues to have a devastating impact on American women. By the end of 2005, an estimated 211,240 women are expected to be diagnosed with breast cancer and nearly 40,410 women will have died of the disease. An estimated 2 million women in the United States have either survived breast cancer or are living with breast cancer today. Breast cancer is responsible for the highest number of new, invasive cancer cases among women each year and is the second leading cause of cancer deaths in women, after lung cancer. The increase in breast cancer incidence that began in the early 1980s continues today, although this increase has slowed dramatically since 1987. Overall, breast cancer mortality rates have shown an encouraging downward trend, dropping 2.3 percent per year from 1990 to 2001 following a slow rate of rise from 1975 to 1990. Breast cancer survival rates have improved by 13 percent since the mid 1970s. Unfortunately, this progress is not impacting all populations equally. Even when controlled for age and stage at diagnosis, black, Hispanic white, and American Indian/Alaska Native women have higher breast cancer mortality rates compared with white and Asian/Pacific Islander women.

In 2004, an internal working group reviewed the NCI's progress in addressing the research priorities identified in the 1998 report of the Breast Cancer Progress Review Group, Charting the Course: Priorities for Breast Cancer Research. The 2004 Breast Cancer Progress Report (*http://planning.cancer.gov/disease/breast.shtml*) documents trends in the NCI breast cancer research portfolio from 1998 to 2003, with progress measures as broad as overall NCI funding levels and as specific as numbers of projects relevant to particular research priorities and examples of research advances.

The report is designed to assist the NCI in accelerating progress against breast cancer by assessing past research and identifying future research needs.

Avon–NCI Progress for Patients Awards Program

A unique public-private partnership between the NCI and the Avon Foundation helps fund innovative translational science at multiple research institutions, supporting early clinical research focused on breast cancer prevention, detection, diagnosis, prediction, prognosis, and treatment. Awards made in 2004 support 11 new projects, including research to evaluate aromatase inhibitors for cancer prevention, estradiol therapy for women with advanced stage disease, and molecular therapies that target the HER2 receptor in metastatic breast cancers.

Breast Cancer SPOREs

Nine breast cancer SPORES (*http://spores.nci.nih.gov/current/breast/breast.html*) conduct collaborative, multidisciplinary research to develop novelagents and technologies for breast cancer treatment and prevention and to identify biomarkers for diagnosis, prognosis, screening, prevention, and treatment. For example, breast cancer SPORE researchers have recently developed an experimental nanotechnology-based system for delivery of molecularly targeted treatment agents directly to cancer cells and demonstrated the safety and modest efficacy of treatment vaccines using peptides from HER-2/neu proteins.

Biology and Genetics

Mouse Models

Researchers from the Mouse Models of Human Cancers Consortium (MMHCC, *http://emice.nci.nih.gov/*) have recently developed models for use in the elucidation of the roles of c-Myc overexpression, transforming growth factor-beta (TGF-β), estrogen receptor status, pregnancy-associated changes, and dietary factors in human breast cancers. These models provide important tools for studying key molecular pathways that might provide targets for therapies through better understanding of tumor growth and metastasis. Modeling breast cancer in mice has also led to the isolation and characterization of functional mouse mammary gland stem cells. This advance may aid in the identification of progenitor cells of different types of mammary cancer.

HER2 and AIB1

Breast tumors exhibiting HER2 overexpression tend to have a poorer prognosis and a lesser response to tamoxifen. The protein, AIB1, is activated via the HER2 signaling pathway and is a co-activator of the estrogen receptor. Evidence suggests that in the presence of AIB1, the therapeutic estrogen receptor inhibition properties of tamoxifen may be attenuated or reversed. Treatment strategies in preclinical testing that target AIB1 and/or HER2 include anti-HER2 vaccines, HER2 inhibitory agents, and drugs to reverse tamoxifen resistance.

Twist

NCI researchers have discovered that Twist, a protein important in early embryonic development, is reactivated in malignancy and plays a crucial role in breast cancer metastasis. Suppression of Twist expression in highly metastatic breast cancer cells inhibits their ability to metastasize and, hence, may be an important therapeutic target.

Biology of Normal Breast Tissue

The NCI supports studies using laser capture microdissection and gene expression profiling of tissue samples obtained from the breasts of women who have various levels of risk for developing breast cancer, but no history of the disease. A better understanding of the biology of normal breast tissue will help researchers to identify early molecular changes that lead to cancer and to develop more effective prevention, early detection, and treatment strategies.

Genetic Epidemiology

The NCI formed the Consortium of Cohorts, which now includes more than 20 cohorts, to address the need for large-scale collaborations for study of gene–gene and gene–environment interactions in the etiology of cancer. In 2003, the consortium launched its first initiative to pool data and biospecimens from ten large cohorts, which include nearly 800,000 research participants, for studies of hormone-related gene variants and environmental factors involved in development of breast and prostate cancer.

Specimen Resources

The Cooperative Breast Cancer Tissue Resource Database (*http://www-cbctr.ims.nci.nih.gov/*) is a web-based "virtual tissue bank" with a central database to track each tissue in the system. Researchers can search this database online and obtain tissues with associated clinical information. The resource has recently also begun to provide tissue microarrays to researchers studying molecular signatures of breast cancer.

Risk Factors

Genetic Factors

Collaborative research teams from the NCI, the Memorial Sloan-Kettering Cancer Center, and Celera Diagnostics recently found a number of single nucleotide polymorphisms (SNPs) related to breast cancer risk in two estrogen receptor genes (ESR1 and ESR2), especially in Ashkenazi Jews, and other SNPs that were protective against breast cancer. Other NCI researchers discovered SNP variants within DNA repair pathways and BRCA1-interacting proteins that may play a low penetrance role in breast cancer risk.

The HER2 polymorphism, I655V may elevate breast cancer risk in some ethnic groups. NCI researchers estimated age-specific breast cancer risk from HER2 I655V based on genetic analysis and family history of 5,318 Ashkenazi Jews from the Washington, DC area. They found an overall 30 percent increase in estimated cumulative risk of breast cancer to age 70 among HER2 I655V carriers compared with noncarriers. The increased risk was most marked for women younger than 50 years with a family history of breast cancer.

Age-related Factors

NCI researchers who analyzed data from a population case control study conducted in Atlanta, GA, between 1990 and 1992, identified a number of risk predictors more strongly or uniquely associated with breast cancer in women less than age 35 years compared with women aged 45 to 54 years. These predictors include African American race, recent use of oral contraceptives, early childbearing (reflecting a short-term increase in risk immediately following birth), and family history of early-onset breast cancer. These findings suggest that breast cancers that develop in very young women may be etiologically as well as clinically distinct.

Reproductive Factors

The Early Reproductive Events and Breast Cancer Workshop, held in February 2003, was attended by epidemiologists, clinicians, basic scientists, and breast cancer advocates. Workshop participants reviewed evidence from epidemiologic, clinical, and animal studies to provide an integrated scientific assessment of the association between early reproductive events and the risk of breast cancer. Findings in these areas were rated by strength of evidence. They identified gaps in research knowledge and provided recommendations for future research. The following findings were rated with the highest strength of evidence: well established evidence for an association between decreased breast cancer risk and early age at first-term birth, increasing parity, and long duration of lactation; no association between increased breast cancer risk and either recognized spontaneous or induces abortions; in animal models pregnancy, estrogen and progesterone combinations, and short-term estrogen exposure are protective against carcinogen-induced breast cancer. In March 2003, the NCI Board of Scientific Advisors and Board of Scientific Counselors reviewed and unanimously approved the workshop findings. The summary report can be viewed at *http://cancer.gov/cancerinfo/ere-workshop-report*.

Diet

Phase II clinical studies of soy isoflavones and green tea compounds for prevention of breast and other cancers are in progress or planned. Soy and tea consumption are both associated with lower incidences of cancers in humans and have demonstrated cancer prevention properties in laboratory and animal studies.

Physical Activity

Data from the Women's Health Initiative (WHI) Observational Study (*http://www.nhlbi.nih.gov/whi/os.htm*), a large prospective cohort study of postmenopausal U.S. women, ages 50 to 79, demonstrate a protective role of even moderate levels of physical activity on breast cancer risk.

Aspirin

Researchers from the NCI-funded Long Island Breast Cancer Study Project (*http://epi.grants.cancer.gov/LIBCSP*) reported findings in 2004 that reinforce previous suggestions that regular aspirin use may reduce breast cancer risk. Women with either estrogen- or progesterone-sensitive tumors, as well as women who took aspirin at least seven times a week for at least 6 months, benefited the most. The NCI-supported Women's Health Study (*http://www.brighamandwomens.org/preventivemedicine/research/whs.asp*) is now assessing the impact of low-dose aspirin and/or vitamin E on women's risk of cardiovascular disease and cancer.

Antibiotics

In 2004, NCI researchers reported finding an association between antibiotic use and increased risk of breast cancer. The magnitude of risk was dependent on the level of antibiotic use. Further research is needed to identify possible cause/effect relationships.

Radiation

NCI researchers examined breast cancer mortality among 69,525 female radiologic technologists certified in the United States from 1926 to 1982. Breast cancer mortality risks were highest among women first employed as radiologic technologists prior to 1940, and declined over time consistent with the dramatic reduction in recommended radiation exposure limits. Risk increased with number of years employed as a technologist prior to 1950, but not with total years worked as a technologist.

Electromagnetic Fields

Researchers from the Long Island Breast Cancer Study Project (LIBCSP, *http://www.epi.grants.cancer.gov/LIBCSP*) reported in June 2003 that they found no association between residential electromagnetic fields and increased risk for breast cancer.

Breast Implants

NCI researchers who analyzed data from one of the largest studies on the long-term health effects of breast implants found no convincing evidence that breast implants have an effect on the development of connective tissue disorders.

Hormones

Researchers from the Women's Health Initiative (WHI, *http://www.nhlbi.nih.gov/whi*) reported in 2002 that the overall risks of estrogen plus progestin hormone replacement therapy for postmenopausal women outweigh the benefits. After 5.6 years of followup, findings included increased risks of breast cancer, heart disease, stroke, and blood clots. In March 2004, the NIH stopped the estrogen-alone arm of the trial, concluding that estrogen alone appears neither to increase nor decrease heart disease, while increasing the risk of stroke, and decreasing the risk of hip fracture. Estrogen did not increase participant's risk of breast cancer during the study period.

Results from a population-based case control study of 1,640 breast cancer patients showed an increase in breast cancer risk associated with oral contraceptive use, especially in women less than age 35 and in women taking preparations containing the highest levels of ethinyl estradiol and/or progestin. These findings suggest that newer, low-potency/low-estrogen oral contraceptives may confer a lower risk of breast cancer than earlier high-potency/high-estrogen versions.

Researchers examined the association of *in utero* exposure to diethylstilbestrol (DES), a synthetic estrogen, and risk of adult breast cancer among a cohort of exposed and unexposed women, followed for an average of 19 years. DES exposure was associated with an increased breast cancer risk among women, aged 40 and older, and was modestly associated with estrogen receptor-positive tumors. Researchers will continue surveillance of this cohort.

In recent study, NCI investigators found that postmenopausal women with high levels of C-peptide, a protein marker of insulin secretion, and C-peptide:fructosamine ratio, a marker of insulin resistance, were more likely to have epithelial hyperplasia or localized breast cancer than women with the lowest levels of these biomarkers. These findings suggest a role for insulin and insulin resistance in breast pathology in postmenopausal women.

Breast Cancer Risk after Hodgkin's Disease

An international team of scientists recently reported that higher radiation doses to the breast during Hodgkin's disease treatment increased risk for future breast cancers. Higher dosages of alkylating agents and higher radiation doses to the ovaries were associated with decreased risk, possibly due to treatment-related premature menopause. Risk levels assessed in the study may not apply to Hodgkin's disease survivors who were treated with more recent therapeutic regimens.

Other Studies of Environmental and Lifestyle Risks

Current research aimed at defining breast cancer risk associated with environmental and lifestyle factors include studies of regional differences in breast cancer rates in the United States; prenatal-to-adult environmental exposures potentially leading to breast cancer; possible relationships between DDT exposure and breast cancer risk, benign breast cancer conditions, and other outcomes among women; the effects of lifetime radiation on breast cancer risk; and the role of residential distance from steel mills, chemical factories, toxic waste sites, and other industries as risk factors for breast cancer.

Registries

The Breast and Ovarian Cancer Family Registries is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of breast and/or ovarian cancers (*http://epi.grants.cancer.gov/CFR/about_breast.html*).

Prevention

Chemoprevention

Several ongoing breast cancer prevention studies are assessing selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene (Evista®). A recent risk–benefit analysis demonstrated that 2 million U.S. women have a sufficiently high breast cancer risk that they might benefit from tamoxifen use without undue risk for side effects. Researchers with the Breast Cancer Prevention Trial (BCPT, *http://www.cancer.gov/clinicaltrials/digestpage/BCPT*) reported findings that tamoxifen helps prevent development of benign breast abnormalities, decreasing risk for precancerous growth and reducing the need for breast biopsy.

The Study of Tamoxifen and Raloxifene (STAR, *http://www.cancer.gov/star*), underway at more than 500 centers across the United States, Puerto Rico, and Canada, has completed accrual of over 19,000 postmenopausal women at increased risk for breast cancer. Data may be available as early as mid-2006. Prior observational evidence has suggested that raloxifene, a SERM used to treat osteoporosis, may help prevent breast cancer.

Aromatase inhibitors (AIs) are compounds that suppress estrogen levels by inhibiting an enzyme necessary for estrogen production. An NCI-sponsored phase II clinical trial will determine the preventive effects of the AI, exemestane, alone or in combination with celecoxib, on mammographic density in postmenopausal women at high risk for invasive breast cancer.

The NCI is also supporting investigator-initiated research to identify potential molecular targets for prevention of human estrogen receptor-negative breast cancer.

Early Detection, Diagnosis, and Prognosis

Imaging Technologies

The NCI is funding research on a variety of technologies for breast imaging, including digital mammography, computer-aided diagnosis, elastography, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, ultrasound techniques, positron emission tomography (PET), single photon emission computed tomography (SPECT), and thermography. Selected studies seek to improve screening techniques for women with dense breast tissue and for women with BRCA mutations.

The Breast Cancer Surveillance Consortium (BCSC, *http://breastscreening.cancer.gov/index.html*) studies breast cancer screening practices and fosters collaborative research to improve the practice of community-based mammography screening. Recent BCSC research found that increasing age, breast density, and the presence of rapidly growing tumors decreased screening accuracy. Hormone replacement therapy, because it increases breast density, also reduced screening accuracy. Related

research has found that a large portion of late-stage breast cancers are detected in women who have not received recommended screening, although a substantial number of diagnoses were made in women who had been screened. This research suggests the need for better early detection methods, as well as for increasing women's use of mammography.

The NCI-supported American College of Radiology Imaging Network (ACRIN) has completed enrollment to its Digital Mammography Imaging Screening Trial (DMIST, *http://cancer.gov/dmist*). This multicenter clinical trial is comparing the diagnostic power of digital mammography to film-based mammography. Researchers will also assess the accuracy of different techniques and instrument types for digital mammography, and factors that affect diagnostic accuracy.

Gene Expression Profiles

Recent NCI-supported testing of a commercially developed 21-gene panel test demonstrated that this method could successfully predict the risk of breast cancer recurrence in a sizable group of patients, as well as which patients would benefit most from chemotherapy. The Oncotype DX was used to analyze the gene expression patterns of fixed, paraffin-embedded biopsy tissue from women with estrogen-dependent, lymph node-negative breast cancer. About one-quarter of patients were assessed to be at high risk for recurrence and likely to benefit from chemotherapy, in addition to tamoxifen, while about half of patients were at low risk and not expected to benefit. A subsequent trial will test whether the Oncotype DX can predict which intermediate risk patients would benefit from chemotherapy.

NCI researchers and partners are performing genetic testing of women in the BCPT to determine whether variations in genes related to estrogen and tamoxifen metabolism might help predict which women are more likely to benefit from tamoxifen therapy.

Protein Biomarkers

Researchers at MD Anderson Cancer Center are exploring whether measurements of the protein Cyclin E, which helps regulate normal cell growth, can be used to predict breast cancer outcomes. Other NCI researchers are studying whether measurement of tumor levels of the proteins, HER2 and AIB1, involved in estrogen regulation, may be useful in predicting the outcome of tamoxifen therapy. Additionally, one member group of NCI's Early Detection Research Network (EDRN) is focusing on developing biomarkers of breast and gynecologic cancers.

Epidemiological Factors

To identify factors that increase a women's risk of dying from breast cancer, NCI researchers analyzed SEER (*http://seer.cancer.gov/*) data for more than 400,000 breast cancer patients diagnosed between 1973 and 2000. Factors associated with increased breast cancer mortality included diagnosis at a younger age, a later stage of disease, or with larger tumors; estrogen receptor-negative tumors status; and Black race.

Treatment

Anti-hormone Adjuvant Therapy

Tamoxifen

Researchers are exploring ways to improve the effectiveness of tamoxifen therapy, combat tamoxifen resistance, and identify alternative therapies. Current regimens of tamoxifen treatments are effective for 5 years, after which tumors develop resistance to the drug. Scientists are attempting to prolong this window of effectiveness by using a second adjuvant in conjunction with, or instead of, tamoxifen.

In two recent clinical trails, a disproportionate number of strokes occurred among women who received tamoxifen, raising concerns that this anti-hormonal agent may be to blame. A recent NCI-funded study, in partnership with Kaiser Permanente Southern California, showed that chemotherapy, but not tamoxifen therapy, was responsible for the observed increase in the risk for stroke.

Aromatase Inhibitors

Recent updates from an international trial show that postmenopausal survivors of early-stage, node-negative and node-positive breast cancer who took the AI, letrozole, after 5 years of tamoxifen, had a reduced risk of cancer recurrence. The rate of distant cancer spread was reduced by 40 percent compared to placebo, and overall survival rates of women who were diagnosed with node-positive

cancers were improved by 39 percent. Survival rates for women with node-negative tumors are still under study.

A phase II SPORE trial will compare the safety, acceptability, and side effects of letrozole (Femara®), versus placebo in postmenopausal women at increased risk for breast cancer recurrence. Recent non-NCI-funded studies suggest that the AI, anastrozole (Arimidex®), may be superior to tamoxifen as a first line, adjuvant treatment and the AI, exemestane, given after two years of tamoxifen, may improve disease-free survival.

RADIATION THERAPY

Scientists from the National Surgical Adjuvant Breast and Bowel Project (*http://www.nsabp.pitt.edu/*) reported in late 2002 that women with very small breast tumors who received both radiation therapy and tamoxifen after surgery had fewer recurrences of cancer in the same breast than women who received either radiation or tamoxifen, but not both.

Conventional Chemotherapies

PACLITAXEL

Adding the drug paclitaxel to standard adjuvant chemotherapy of adriamycin and cytoxan improved disease-free survival by 17 percent in women with node-positive breast cancer, according to clinical trial results. Women receiving a dose-dense chemotherapy regimen benefited the most. As a result of this discovery, 4,000 more women could be alive and disease-free 4 years after diagnosis.

AGE EFFECTS

In 2003 NCI-sponsored NSABP researchers reported that post-operative chemotherapy can improve outcomes in women diagnosed with estrogen receptor-negative, node-negative breast cancer. More recently, NSABP investigators reported that benefits from post-operative chemotherapy with either cyclophosphamide plus methotrexate and 5-fluorouracil or doxorubicin with cyclophosphamide were greater, the younger the age of the patient. Also, premenopausal women experienced a greater recurrence-free survival benefit than postmenopausal women.

EFFECTIVENESS OF DIFFERING TREATMENT REGIMENS

The NCI is sponsoring clinical trials for breast cancer treatment to compare the effectiveness of four different treatment schedules using the drugs doxorubicin, cyclophosphamide, and paclitaxel in treating patients who have undergone surgery for breast cancer.

Immune Therapy

NCI researchers have found promising evidence that immune cell transplant therapy can help shrink tumors of metastatic breast cancer. Partial or minor responses, lasting an average of 3 months, were seen in six of the 16 treated breast cancer patients. However, more research is needed to lower toxic graft-versus-host effects and improve treatment response.

Radiation Therapy

The NCI is conducting a clinical trial of partial-breast irradiation to test whether this technique is equivalent to irradiation treatment of the whole breast.

Monoclonal Antibodies

Herceptin®, a monoclonal antibody that binds to HER2, has been approved by the FDA for treatment of metastatic breast cancer. However, less than 35 percent of patients with HER2-overexpressing metastatic breast cancer respond to herceptin. Researchers have now shown that PTEN deficiency is a powerful predictor for herceptin resistance. This finding may help guide treatment choices for patients with PTEN-deficient tumors. In other work, NCI researchers are developing potential breast cancer treatment strategies that use monoclonal antibodies to target apoptosis-inducing death receptors located on cancer cells.

Novel Compounds

Researchers supported by NCI preclinical research programs are helping to develop novel compounds that may be effective for breast cancer treatment. These include parthenolide, an anti-angiogenic compound produced by medicinal plants; a synthetic improvement of a naturally occurring anti-tumor antibiotic; and a synthetic compound derived from a marine sponge.

Cancer Control, Survivorship, and Outcomes Research

Education Outreach

In partnership with the Centers for Medicare and Medicaid Services (CMS) and the National Asian Women's Health Organization, the NCI adapted, tested, and disseminated nationally an Asian American/Pacific Islander mammography education resource. This brochure targets Chinese, Vietnamese, and Pacific Islander women in their 40s and older (*http://www.cancer.gov/cancertopics/breasthealth*).

Researchers funded by the NCI and the Agency for Health Care Research and Quality (AHRQ) are studying how to communicate benefits and limitations of breast cancer screening tests; developing tools to help women ask themselves important questions and make informed decisions about screening; and exploring new communication technologies, including online and other interactive health communications tools to address women's concerns.

The NCI's Office of Education and Special Initiatives has produced the booklet, *Surgery Choices for Women with Early-Stage Breast Cancer*, in partnership with several federal agencies and offices and the National Research Center for Women and Families. This booklet (*http://www.cancer.gov/cancertopics/breast-cancer-surgery-choices*) helps women weigh surgical options for early-stage breast cancer and take a more active role in their treatment.

The NCI is participating in the DHHS Initiative on Breast Cancer Prevention and Education to consolidate departmentwide information on breast cancer in one web location. Designers anticipate launching the website in 2005.

Survivorship Research

NCI-funded and other researchers have shown exercise programs or training to positively impact cardiopulmonary function, quality of life, levels of fatigue, and functional ability in breast cancer survivors. Exercise, in combination with group psychotherapy, appears to improve women's quality of life beyond the benefits received from group participation alone, particularly in relation to physical and functional outcomes. Behavioral interventions also appear to have enormous appeal to survivors eager to reduce the perceived stress in their lives and to "take control" of their bodies after cancer.

Health Disparities

While white women have the highest rate of breast cancer, African American women have the highest death rate of all races from the disease. Researchers funded by the NCI and the U.S. Department of Defense have found that African American women are much more likely than white women to be diagnosed with aggressive breast cancer and to carry alterations in the tumor suppressor gene, p53. More research is needed to identify potential implications of racial/ethnic differences in p53 alterations on breast cancer mortality rates.

A study linking data from NCI's SEER databases and Medicare data have revealed that disabled women with breast cancer are diagnosed at a later stage of disease than nondisabled women, with the disparity greater for women with fee-for-service coverage compared with HMO coverage.

Cervical Cancer

An estimated 10,370 cases of invasive cervical cancer are expected to be diagnosed in the United States in 2005 and 3,710 women are expected to die from the disease. Incidence and mortality rates have decreased steadily over the past five decades, largely due to the widespread use of the Papanicolaou test (Pap smear) which detects cervical cancer and precancerous lesions. The Pap smear has made cervical cancer one of the most preventable cancers, but older, poorer, and less-educated women are less likely to be screened and screening is not available in many low-resource regions of the world. Worldwide, cervical cancer has a significant impact with nearly 500,000 new cases and nearly 250,000 deaths reported annually.

Cervical Cancer SPORE

The SPORE for cervical cancer research, located at the Johns Hopkins University School of Medicine, includes integrated projects for identification of biomarkers for cervical cancer progression; development of vaccines for cervical cancer prevention and

treatment; and development of antigen-specific cancer immunotherapies and anti-angiogenesis agents for treatment of advanced cervical cancer. The SPORE also facilitates career development of individuals with an interest in translational cervical cancer research.

Risk Factors

Human Papillomavirus

Although oncogenic human papillomavirus (HPV) infections are common and usually clear within 1 to 2 years, infection with certain HPV subtypes is now recognized as the major cause of cervical cancer. Virtually all cases of cervical cancer worldwide are caused by a group of approximately 15 HPVs, with HPV types 16 and 18 accounting for approximately 70 percent of all cases.

In prior research to identify co-factors for cervical cancer risk among HPV-infected women, HPV infection was identified by DNA testing. Because this technique detects only current infection, NCI researchers conducted a study using seropositivity to five oncogenic HPV types as a marker of past exposure. Independent, significant predictors of seropositivity among uninfected controls included numbers of sexual partners, Black race, and oral contraceptive use. Condom use was protective. Among HPV-exposed women, Papanicolaou screening, black race, and yeast infection were significantly associated with reduced cancer risk. Significant predictors of increased risk included smoking, low education and income, and history of nonspecific genital infection. In contrast to previous findings, oral contraceptive use was unrelated to cervical cancer risk and multiparity was only weakly related to risk.

The NCI is supporting large, population-based cohort studies, including the Guanacaste Study of HPV Natural History study in Costa Rica and the Portland Kaiser Permanente cohort study in the United States, to better define risk factors for progression of precancerous lesions among HPV-infected women. The Costa Rican study will assess the various roles of mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV. The U.S. study is investigating specific immune responses to viral infection and risk of persistence and/or progression of lesions. Researchers will test *in vitro* biological specimens for immunological markers that may correlate with disease status over time.

NCI researchers recently published *Future Directions in Epidemiologic and Preventive Research on HPV and Cancer*, a monograph of forward-thinking commentaries written by senior epidemiologists and their interdisciplinary colleagues. This monograph was published in the *Journal of the National Cancer Institute* in followup to a 2002 meeting held at the NCI, where the authors discussed topics including the natural history of HPV, immunosuppression, vaccines, co-factors that promote cancer, and descriptive epidemiology.

Human Immunodeficiency Virus

Women with human immunodeficiency virus (HIV) are often co-infected with HPV, and HPV infection is more likely to be persistent and less likely to regress in HIV-positive than HIV-negative women. Women positive for both HIV and HPV also have a 6.8-fold greater risk of invasive anal cancer than HIV-negative/HPV-positive women.

Human Leukocyte Antigen

NCI investigators are exploring the relationship between human leukocyte antigen (HLA) class I alleles and cervical neoplasia in a subset of participants in three large U.S. and Costa Rican studies. Findings are consistent with previous hypotheses that a single HLA allele may be sufficient to protect women from progression of early precancerous lesions and suggest that natural killer cell function may play a role in HPV infection and cervical neoplasia.

Tobacco

According to the 2004 Surgeon General's report on the health consequences of smoking, there is sufficient evidence to support a causal relationship between smoking and cervical cancer. In a recent, large cohort study of HPV-infected women, smoking increased the risk of cervical precancer and cancer twofold. Smoking after a cervical cancer diagnosis shortens survival time, increases risk of recurrence and the development of another primary tumor, reduces treatment efficacy, and increases treatment complications. Even so, one third of patients

who smoked prior to their diagnosis continue to smoke after their diagnosis.

DES

The NCI continues to follow cohorts of women and their offspring exposed to DES during pregnancy. Recent analysis of data from the DES Follow-up Study has shown no excess risk of cancer overall in DES-exposed offspring, compared with levels of risk for the general population, as calculated from SEER data. Preliminary data from the Third Generation Study, which will assess DES-related cancer risk in women whose mothers were exposed to DES *in utero*, shows no effects of DES on age at menarche or menstrual irregularity. The NCI maintains a web-based DES reference for clinicians at *http://www.cancer.gov/cancerinfo/persons-exposed-to-des*.

Prevention

HPV Vaccine

The NCI and partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. NCI researchers have designed a promising recombinant vaccine composed of HPV virus-like particles. Merck and GlaxoSmithKline (GSK) have licensed this vaccine technology from NIH and are developing vaccines that target HPV types 16 and/or 18. In early phase I and II clinical trials, these vaccines have conferred near complete protection (94 to 100 percent), in fully vaccinated women, against persistent infection by the HPV type(s) targeted. Phase III clinical trials are in progress. The NCI and public health research partners are conducting a parallel efficacy trial of the GSK vaccine in Costa Rica, where cervical cancer is the most common malignancy in women.

Obesity

NCI scientists evaluated whether obesity, which can influence hormone levels, plays a role in adenocarcinoma and/or squamous cell carcinoma of the cervix. Researchers found a positive association between height, weight, body mass index, and weight-to-hip ratio and adenocarcinoma. Higher BMI and WHR were associated with more advanced disease stage at adenocarcinoma diagnosis, even among recently and frequently screened patients. Associations between BMI and WHR with squamous cell carcinoma were weaker, and no association was found for height or weight.

Early Detection, Diagnosis, and Prognosis

Pap Smear Screening

In 1987, approximately 73 percent of women, aged 18 and older, had a Pap smear within the past 3 years, and by 2000, 81 percent of women ages 18 and older had a Pap smear within the past 3 years. This includes 77 percent of Hispanics, 84 percent of Blacks, and 82 percent of whites.

Imaging

NCI-supported researchers are developing fluorescence and reflectance spectroscopic imaging technologies to detect cervical neoplasia. Early clinical testing has shown that the imaging techniques are feasible in large populations and can be used at any time during the menstrual cycle except during menstruation. Trial participants reported significantly less pain and anxiety and were more satisfied with spectroscopy than with the usual care procedures. Research is ongoing to test the accuracy and reproducibility of this detection technique.

HPV Testing

Researchers have demonstrated that HPV DNA detection predicts increased risk of cervical precancers and cancers that may develop up to several years following testing. It can be used to detect high-grade cervical neoplasia, and is more sensitive than cytologic methods for detecting HPV infection in its earliest, as well as latter, stages. Findings from a large study suggest that HPV testing in combination with Pap smear testing may safely permit longer screening intervals among patients with negative results for both measures. These results were incorporated into recent FDA licensure of HPV DNA testing as an adjunct for Pap smear screening. Findings from a related study suggest that 15 percent of women in annual cervical screening programs, who have a negative Pap smear and a positive oncogenic HPV test, will have a subsequent abnormal Pap smear within

5 years. These findings support the use of HPV DNA testing as a highly sensitive screening test.

The NCI-funded ASCUS-LSIL Triage Study (ALTS, *http://www3.cancer.gov/prevention/alts/index.html*) demonstrated that HPV DNA testing can be used to triage equivocal Pap test interpretations. There are more than 2 million such results per year in the United States. HPV DNA negativity implies very low risk of cervical precancer or cancer.

Another study is using computer-based modeling of the health benefits and cost-effectiveness of preventive HPV vaccination and screening strategies. Findings suggest that vaccination initiated at age 12, followed by cytology screening for HPV every 3 years beginning at age 25, may be the most cost-effective strategy. This approach was estimated to reduce cervical cancer mortality by 94 percent compared with no intervention.

Treatment

Chemoradiation

Five randomized phase III trials all have shown a significant overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy for treatment of cervical cancer patients. In these trials, which varied somewhat in terms of stage of disease, dose of radiation, and schedule of cisplatin and radiation, the risk of death from cervical cancer was decreased by 30 to 50 percent by concurrent chemoradiation.

Treatment-related Side Effects

Researchers are examining the efficacy of drugs to alleviate or prevent side effects of cervical cancer treatment, including treatment-induced anemia and quality-of-life changes.

Cancer Control, Survivorship, and Outcomes Research

Psychosocial Issues

The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, social, and biomedical research on the interrelationships between cognition, emotion, biological processes, and physical health in patients affected by cancer, including women at high risk for cervical cancer due to co-infection with HIV and HPV. An NCI-supported study is looking at behavioral and immunologic components that correlate with psychological distress and coping in women diagnosed with mild dysplasia of the cervix caused by HPV infection.

Sexuality Issues

Several studies are under way to assess sexual function and general quality of life for women receiving treatment for different stages of cervical cancer.

Health Disparities among Special Populations of Women

Access to Health Care and Screening

The NCI Center to Reduce Cancer Health Disparities (CRCHD) has an ongoing program to address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas (*http://crchd.nci.nih.gov/initiatives/#Reducing*). Women most affected include African American women in the South, Latino women along the Texas–Mexico border, white women in Appalachia, American Indians of the Northern Plains, Vietnamese American women, and Alaska Natives. A report, Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities, will be released in the spring of 2005. The report offers recommendations for improving elements of the health system, particularly publicly funded health services.

The NCI's Cancer Information Service is collaborating on a project focused on reducing cancer health disparities among women rarely or never screened for cervical or breast cancer, in partnership with the Centers for Disease Control and Prevention (CDC) and the American Cancer Society. This public–private partnership is working with regional and local public health practitioners and stakeholders from eight Appalachian states with the highest cervical and breast cancer mortality and the lowest screening rates for these cancers.

In cooperation with the CRCHD and the Deep South Network for Cancer Control, NCI researchers are conducting a study of cervical cancer screening in the Mississippi Delta using self-collected cervical specimens tested by sensitive HPV DNA assays. The study will determine whether self-testing for HPV can be used to screen women reluctant or unable to obtain Pap tests.

The NCI is also piloting the Patient Navigator Program (*http://www3.cancer.gov/rrp/CDRP/navigator.html*) to provide patients with social service case management to help them navigate the healthcare system to receive prompt follow-up care after an abnormal cervical cancer screen or diagnosis. This program directly addresses an NCI Gynecologic PRG recommendation for a navigator program.

Surveillance

A recent study suggests that census-based socioeconomic measures, such as geographic area, income, and education levels, could serve as important surveillance tools for monitoring temporal trends in cancer-related health inequalities and targeting interventions.

Ovarian Cancer

In 2005, approximately 22,220 women in the United States are expected to be diagnosed with ovarian cancer, and approximately 16,210 are expected to die of the disease. Incidence rates decreased by 0.8 percent per year between 1985 and 2001. Ovarian cancer is responsible for the highest mortality rates of all gynecologic cancers. Incidence and mortality rates are highest in white women compared to other racial and ethnic groups. When detected early, ovarian cancer is highly treatable, with a 5-year survival rate of 95 percent. Ovarian cancer is often asymptomatic in its early stages, and symptoms that do occur are often not of the type that would alert most women or their health care providers. Thus, most diagnoses occur at advanced stages of disease, when survival rates are 69 percent for regionally advanced stages and 29 percent for stages with distant metastases.

Ovarian Cancer SPOREs

The NCI's five Ovarian Cancer SPOREs (*http://spores.nci.nih.gov/current/ovarian/ovarian.html*) frequently collaborate to develop prognostic, screening, prevention, and therapeutic tools for ovarian cancer. Biomarkers under study for the early detection of ovarian cancer include CA-125, mesothelin, HE4, apolipoprotein A1, transthyretin, and inter-alpha-trypsin inhibitor heavy chain H4. Examples of other ovarian cancer SPORE research include clinical trials of the monoclonal antibody, TRA-8, for treatment of breast and ovarian cancer and development of therapies that target the phosphatidylinositol 3 kinase (PI3K) pathway, which is frequently mutated in ovarian cancer.

Biology

Mouse Models

Development of genetically engineered mouse models of ovarian epithelial cancer is challenging due to the unusual properties of ovarian surface epithelium, the proposed cell of origin for these malignancies, and the need for a cell-type-specific promoter to drive gene expression. NCI-supported researchers recently developed a model with deficiencies in expression of the tumor suppressor genes, p53 and Rb, which are frequently lost or mutated in ovarian cancer. These mice quickly succumbed to aggressive ovarian cancer and many of the cancers were associated with notable characteristics of the human disease. In another model the powerful T-antigen oncogene was incorporated in the ovarian epithelium by use of a special promoter, resulting a poorly differentiated form of ovarian cancer typical of late-stage human ovarian cancer.

Other NCI-supported researchers developed a mouse model that mimics estrogen receptor positive, invasive, metastatic endometrioid ovarian adenocarcinoma by activating an oncogenic K-ras and conditionally deleting the tumor suppressor, PTEN. This model will be valuable for preclinical studies of selective estrogen receptor modulators as well as other conventional chemotherapeutic agents.

Researchers recently improved a rat model of human ovarian cancer by using a much lower dose of the initiating carcinogen. This improved model exhibits characteristics of the human disease, including preneoplastic and early neoplastic lesions, point mutations in p53 and K-ras genes, and overexpression of the estrogen and progesterone receptors. This model should permit study of the role of hormone receptors and genetic alterations in tumor etiology and progression and provide a platform to test novel interventions.

Vascular Endothelial Growth Factor

NCI researchers have discovered that women with ovarian cancer who had a greater sense of well being had markedly lower blood levels

of vascular endothelial growth factor (VEGF), a stress-related cytokine that stimulates angiogenesis. This research suggests that effects on VEGF may be one way that biobehavioral factors affect ovarian cancer progression.

Risk Factors

In the United States approximately one woman in 70, or 1.4 percent, will develop ovarian cancer during her lifetime. Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the single greatest risk factor is a family history of the disease. Three inherited ovarian cancer susceptibility syndromes have been described: 1) familial site-specific ovarian cancer, 2) familial breast/ovarian cancer, and 3) Lynch II syndrome (combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers). It is believed that 5 to 10 percent of ovarian cancers are caused by inherited mutations in the BRCA1 or BRCA2 genes.

Infertility/Fertility Drugs

NCI researchers identified a higher rate of ovarian cancer incidence in a cohort of 12,193 women evaluated for infertility between 1965 and 1988, compared to incidence rates for the general female population. Among this group, risk was higher for patients with primary than those with secondary infertility, particularly for those who never subsequently conceived, and was highest in patients with endometriosis. No evidence that either of the two commonly used fertility drugs, clomiphene and gonadotrophins, increased risk for ovarian cancer. Researchers will continue monitoring the cohort for possible long-term risks.

Inherited Risk Factors

In a recent NCI study, researchers found that the levels of ovarian cancer risk reduction associated with gynecologic surgery are similar for women carrying BRCA1 and BRCA2 mutations and non-carriers of these mutations.

Registries

The Breast and Ovarian Cancer Family Registries (*http://epi.grants.cancer.gov/CFR/about_breast.html*) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of breast and/or ovarian cancers.

Prevention

Oral contraceptive use, having had at least one full-term pregnancy, and having breast fed are associated with a reduced risk of ovarian cancer. Tubal ligation and hysterectomy may be associated with a decreased incidence of ovarian malignancy. HRT in postmenopausal women may be associated with an increased risk of developing ovarian cancer.

The NCI is sponsoring a multicenter clinical trial that will quantify the extent of cancer risk reduction after preventive removal of the ovaries and fallopian tubes and will assess quality of life and incidence of noncancer diseases related to premature menopause. Researchers will also evaluate a novel approach to ovarian cancer screening based on quantitative assessment of changes in the tumor marker, CA-125, over time.

Early Detection, Diagnosis, and Prognosis

Proteomics

Researchers from the FDA/NCI Clinical Proteomics Program (*http://home.ccr.cancer.gov/ncifdaproteomics/ppatterns.asp*), Correlogic Systems Inc., and the Frederick Cancer Research Center Biomedical Proteomics Program (*http://web.ncifcrf.gov/rtp/prot/site/default_flash.asp*) are refining a proteomic profiling technique for early detection of ovarian cancer. In a preliminary trial, this test identified, with 100 percent sensitivity and 100 percent specificity, 68 women previously diagnosed with ovarian cancer and 43 women who were cancer free. Researchers will conduct a multi-institutional clinical trial to investigate the method's ability, when used in large numbers of patients and by multiple operators, to distinguish between blood samples from women with recurrent ovarian cancer and those who are cancer free. This research addresses a Gynecologic Cancers PRG recommendation to develop proteomic technologies for early detection of ovarian cancer.

NCI intramural researchers, in collaboration with selected SPORE and EDRN member institutions, will develop a repository of serum

samples collected from women in first clinical remission of advanced ovarian cancer. These samples will be used to develop and test proteomic and biomarker panels for detecting minimal residual disease.

National Ovarian Cancer Early Detection Program: Screening and Genetic Study

This multisite clinical trial seeks to identify effective screening and genetic testing methods to identify women at increased risk for developing ovarian cancer; identify and develop highly sensitive and specific early detection tumor markers; develop therapies based on molecular, genetic, and biochemical insights; and determine the utility of minimally invasive office diagnostic laparoscopy and the "Ovarian Pap Test" (*http://www.clinicaltrials.gov/ct/gui/show/NCT00005095*).

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial

Screening for ovarian cancers, one component of the PLCO trial, includes a physical examination of the ovaries, a blood test for the tumor marker CA-125, and transvaginal ultrasound in healthy women, ages 55 to 74 (*http://dcp.nci.nih.gov/plco*). Analysis of the results of screening tests done in the first year of the PLCO will be published in 2005.

Treatment

New Drug Strategies

Standard post-surgery chemotherapy for newly diagnosed ovarian cancer usually consists of treatment with paclitaxel and/or a platinum-based drug (e.g., carboplatin or cisplatin). Patients whose disease recurs more than 6 months after completion of chemotherapy are usually re-treated with a platinum-based drug. In 2003, NCI clinical trial researchers reported that patients treated with a combination of paclitaxel plus platinum-based drugs lived a *median* of 5 months longer than those who received a platinum-based drug alone. Both groups of women experienced the same quality of life.

NCI-supported investigators are exploring the effectiveness of various drug combinations and treatment regimens for treating advanced stage and recurrent ovarian cancer. Drugs currently in clinical testing include bortezomib, docetaxel, erlotinib, gemcitabine, ixabepilone, liposomal doxorubicin, nitrocamptothecin, oxaliplatin, sorafenib, TLK286, and topotecan. Innovative approaches to the treatment of advanced ovarian cancer in development or in early trials include therapeutic vaccines, monoclonal antibody therapies, donor lymphocyte infusion, nonmyeloablative allogeneic transplantation, gene therapy, and antiangiogenic agents.

Endometrial Cancer

Cancer of the corpus uteri, or endometrium, is the fourth most common invasive cancer among women in the United States. An estimated 40,880 American women will be diagnosed with uterine cancer in 2005, and approximately 7,310 will die from the disease. The incidence of endometrial cancer declined from 1975 to 1988, increased slightly over the next decade, and has begun again to decline. Average incidence rates for white women were 26.1 per 100,000 from 1992 to 2001, while incidence rates for African American women were significantly less at 18.0 per 100,000. Average mortality rates show an opposite trend, with the mortality rate for white women at 3.9 per 100,000 and mortality rates for African Americans nearly double that at 7.0 per 100,000.

Gynecologic Cancer SPORE

The Gynecological Cancer SPORE at the University of Texas M.D. Anderson Cancer Center, first funded in 2003, conducts innovative translational research for the prevention and treatment of uterine tumors. Major projects of the SPORE aim to:

- Decipher the fundamental molecular differences between type 1 and type 2 endometrial cancers;
- Provide a panel of molecular markers that will be useful in endometrial cancer prognosis and in identifying patients at risk for developing the malignancy;
- Dissect the molecular pathways involved in estrogen- and progesterone-mediated growth regulation of the uterine endometrium and smooth muscle;

- Promote novel strategies in the chemoprevention of endometrial cancer; and
- Understand, at the molecular level, the complex mechanism of action of selective estrogen receptor modulators (SERMs), such as tamoxifen, raloxifene, and a new third-generation SERM, Arzoxifene, in the epithelial and smooth muscle compartments of the uterus.

Biology

Microsatellite Instability

Approximately 20 percent of endometrial cancers demonstrate microsatellite instability (MSI), which is the abnormal expansion or contraction of small repetitive DNA sequences due to defects in the DNA mismatch repair pathway. The NCI supports research to determine the cause of MSI in endometrial tumors. Emerging insights into the initiation of endometrial cancer may help in the development of targeted therapies that will benefit patients with this disease.

Gene Expression Profiling

NCI researchers have discovered differences in gene expression among histologic types of endometrial cancers and normal endometrium, and between serous and endometrial cancer tissues. Other NCI-supported researchers discovered two highly distinct molecular subtypes that help define estrogen-dependent and estrogen-independent endometrial carcinoma. This research provides the basis for investigation of previously unrecognized novel pathways involved in the development of endometrial cancers and addresses a recommendation of the NCI Gynecologic PRG to identify genetic and molecular signatures of endometrial cancer.

Specimen Resources

The Gynecologic Oncology Group tissue bank provides specimens for researchers studying endometrial cancer. Requests for tissues are assessed by peer review. The Tissue Expediter and the Specimen Resource Locater website (*http://pluto3.nci.nih.gov/tissue/default.cfm*) can assist researchers to identify sources of tissue.

Mouse Models

NCI researchers generated a mouse model of endometrial carcinoma by regulating the expression of the tumor suppressor gene, PTEN, and one of the mismatch repair genes, MLH1. These mice develop invasive carcinoma closely resembling the human disease.

Risk Factors

An increased risk for endometrial cancer has been associated with estrogen-only hormone therapy, personal history of breast cancer, tamoxifen use, obesity, age, lack of physical activity, HNPCC, and diabetes and other medical conditions, but possible mechanisms remain obscure. Cigarette smoking and high intake of complex carbohydrates appear to reduce risk. Recent research suggests that family history of breast cancer may not be associated with increased risk for endometrial cancer.

Diet

Researchers with an NCI-supported, case-control study in Shanghai, China found that regular consumption of soy protein or soy isoflavones was inversely associated with the risk of endometrial cancer, especially among women with high body mass index and high waist:hip ratio. An NCI-funded, case-control study based in the greater San Francisco Bay area found an association between consumption of some phytoestrogenic compounds (isoflavones, coumestans, and lignans) at levels typical of an American-style diet, and reduced risk of endometrial cancer.

Menstrual and Reproductive Factors

NCI-supported researchers evaluated the association of menstrual and reproductive factors with the risk of endometrial cancer in a population-based, case-control study conducted in urban Shanghai. Findings suggest that prolonged menstruation was related to an increased risk of endometrial cancer while pregnancy, full-term and interrupted, reduced the risk of endometrial cancer.

Tamoxifen

Tamoxifen, used in the prevention and treatment of ER-positive breast cancer, has been linked with an increased risk of endometrial cancer. Studies indicate that tamoxifen may have delayed effects, such as the increased risk of rare but aggressive uterine tumors of unclear pathogenesis. New drugs, such as aromatase inhibitors, that can be used alone or in combination with tamoxifen

for treatment of hormone-dependent tumors are being investigated.

Insulin-like Growth Factor

NCI researchers found an inverse association between development of endometrial cancer and certain serum insulin-like growth factors (IGF-1, 2) and an insulin-like binding protein (IGFBP-3) in a case-control study of postmenopausal women with endometrial cancer and matched population-based controls. Further research is needed to explore the potential role of the IGF system in endometrial carcinogenesis and proliferation.

Prevention

NCI prevention studies are focusing on developing breast cancer prevention and treatment agents that do not increase endometrial cancer risk; developing chemoprevention methods for endometrial cancer; and determining the effects of obesity and nutrition on endometrial cancer. A Phase 2 randomized study comparing medroxyprogesterone and ethinyl estradiol and norgestrel for the prevention of endometrial cancer in HNPCC patients is ongoing.

Early Detection, Diagnosis, and Prognosis

NCI-supported researchers have discovered a strong correlation between methylation of ribosomal DNA (rDNA) in endometrial tumors and risk of recurrence. The NCI is funding a new study to confirm this observation and to develop a high-throughput assay for rDNA methylation that may help identify women with high risk of recurrence who would benefit from adjuvant therapy, in addition to surgery.

Treatment

Surgery, including hysterectomy and bilateral salpingo-oophorectomy, is the most common treatment for endometrial cancer. Researchers are identifying adjuvant chemotherapy regimens that can improve survival in women with endometrial cancer. In women who have not completed childbearing, alternative treatments that address fertility issues are being investigated.

Chemotherapy

The NCI-funded Gynecologic Oncology Group (GOG; *http://www.gog.org/*) conducts research focused on women with pelvic malignancies, including endometrial cancer. In a recent phase III GOG clinical trial, post-surgical adjuvant chemotherapy with cisplatin and doxorubicin improved survival by 33 percent in women with advanced endometrial cancer, compared to women who were treated with standard radiation treatment. The GOG is also examining the potential role of paclitaxel (Taxol®) as a treatment agent, either singly or in combination with other agents, such as megestrol acetate and medroxyprogesterone acetate.

Radiation Therapy

In a recent GOG clinical trial, researchers concluded that adjunctive radiation therapy in early-stage, intermediate-risk endometrial carcinoma decreases the risk of recurrence, but should be limited to patients whose risk factors fit a high intermediate-risk definition.

Hormonal Therapies

The NCI is conducting a phase II pilot study to compare the efficacy of medroxyprogesterone in patients with progesterone receptor-positive versus progesterone receptor-negative endometrial adenocarcinoma of the uterine corpus.

Combined Modality and Targeted Therapies

The NCI supports studies comparing different chemotherapies, alone or in combination, and with or without radiotherapy. Most trials are in Phase I or II. Studies are also in progress to test the effectiveness of the molecularly targeted agents, trastuzumab (Herceptin®), bevacizumab (Avastin™), lapatinib (GW572016), and sorafenib (BAY 43-9006) for treating endometrial cancer. Side effects of therapy and quality-control issues in radiation equipment are also being investigated.

Lung and Other Tobacco-related Cancers

The 2004 Surgeon General's report, The Health Consequences of Smoking (*http://www.cdc.gov/tobacco/sgr/sgr_2004/*), estimates that smoking tobacco causes 159,600 cancer deaths each

year. Research shows that tobacco use causes an increasing number of cancers of particular concern to women, including lung, cervical, and ovarian. Scientific evidence is also suggestive of a causal relationship between smoking and colorectal adenomatous polyps and colorectal cancer. Epidemiological studies exploring a possible link between smoking and breast cancer have yielded inconclusive results, although animal, human biomarker, and *in vitro* cellular studies strongly suggest that tobacco carcinogens may be involved in breast cancer development. Tobacco use also causes leukemia and cancers of the bladder, esophagus, kidney, larynx, oral cavity, pancreas, and stomach.

Since 1987, more women have died each year of lung cancer than of breast cancer, which had been the major cause of cancer death in women for more than 40 years. It is estimated that 79,560 women will be diagnosed with lung cancer in 2005 and 73,020 women will die from this disease in the United States. Although incidence and mortality rates in men have been declining since the early 1980s and 1990s, respectively, these rates for women have continued to increase until recently. The latest analysis of SEER data shows a decline in incidence rates, from 1998 to 2001, and stabilization of mortality rates since 1995. Declining incidence rates appear to be a result of reductions in cigarette consumption. High mortality rates reflect our limited ability to detect lung cancer at an early and potentially more curable stage. Over half of new cases are diagnosed in advanced stages of the disease, for which the 5-year relative survival is only 3.3 percent. With the exception of Asian/Pacific Islander (API) patients, the chance of dying from lung cancer was 4 to 23 percent higher from 1998 to 2001 in minority populations compared with non-Hispanic white patients. Survival rates for API women diagnosed with lung cancer were comparable to those for non-Hispanic whites.

Women, Tobacco, and Cancer

The NCI has taken the lead in a public/private partnership to address the high rate of tobacco-related cancers in women. A working group meeting, held in February 2003, Women, Tobacco, and Cancer: An Agenda for the 21st Century, assembled researchers, clinicians, and members of the advocacy community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. The working group released their report (*http://searchosp1.nci.nih.gov/whealth/reports/wtobacco.pdf*) in July 2004, recommending strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, and evaluation and surveillance that will contribute to reducing and, ultimately, eliminating the harmful health effects of smoking in women.

Lung Cancer Integration and Implementation Team

The NCI has created the lung cancer Integration and Implementation (I2) team to address the recommendations of the NCI's Lung Cancer Progress Review Group (PRG, *http://prg.nci.nih.gov/pdfprgreports/2001lung.pdf*). The I2 team, an internal working group, will inventory the NCI's current lung cancer research portfolio and analyze strategies for implementing PRG recommendations. Team members will use this analysis to identify three to five high-impact, focused initiatives to reduce lung cancer mortality rates and identify potential collaborations to advance lung cancer research.

Transdisciplinary Tobacco Use Research Centers (TTURCs)

TTURCs (*http://dccps.nci.nih.gov/tcrb/tturc*) help provide the needed infrastructure for tobacco research across many disciplines and address an NCI Lung Cancer PRG recommendation to continue research on the genetic, social, and biobehavioral aspects of tobacco control. NIH has announced nearly $12 million in new TTURC funding to be awarded over the next 5 years by the NCI, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism. A group of seven TTURCs will study a range of topics, including genetic and psychological factors that influence tobacco use and addiction; effective smoking cessation treatments; molecules or genes that could affect tobacco exposure and disease risk; and public health impact of regional and national tobacco control policies.

Lung Cancer SPOREs

The NCI currently funds seven lung cancer SPOREs (*http://spores.nci.nih.gov/current/lung/lung.html*). The Lung SPORE at the University of Pittsburgh Cancer Institute has a focus on improving detection and treatment of lung cancer and understanding the mechanisms of women's susceptibility to lung cancer. Researchers at this SPORE are investigating the role of estrogen receptors in lung cancer in women. A clinical trial is planned to explore possible protective effects of administering estrogen receptor antagonists to lung cancer patients.

Risk Factors

Tobacco

Results from two cohort studies, the Nurses' Health Study (*http://www.channing.harvard.edu/nhs/*) and the Health Professionals Follow-Up Study of men, indicate that men and women with comparable smoking histories have similar risks of developing lung cancer. Previous case-controlled studies have suggested that women are at greater risk.

A multicenter case-control study of lung cancer and tobacco use is ongoing in Milan, Italy. This trial includes collection of extensive questionnaire and biospecimen data, and is unique in collecting information on many other factors, including tumor tissue obtained in surgery, demographics, tobacco use, alcohol use, occupational exposures, diet, and medical illness.

The PLCO (*http://www3.cancer.gov/prevention/plco/*) and the Shanghai Women's Health Study (*http://epi.grants.cancer.gov/ResPort/ShanghaiWomen.html*) are large, ongoing cohort studies that include biospecimens and questionnaire data with a focus on tobacco-related cancers.

The NCI supports transdisciplinary research on the interplay of behavior, chemistry, toxicology, biology, and epidemiology to determine the cancer risk potential of reduced-exposure tobacco products (*http://grants.nih.gov/grants/guide/pa-files/PA-04-103.html*). Current scientific evidence is insufficient to evaluate whether these new products actually reduce the user's exposure or risk for tobacco-related diseases.

Radon

NCI researchers pooled data from two large case-control studies of residential radon conducted in China to show that long-term radon exposure, at concentrations found in many homes, appears to increase lung cancer risk.

Diet

In follow-up study to the Beta-Carotene and Retinol Efficacy Trial (CARET), researchers at the Fred Hutchinson Cancer Research Center confirmed that beta-carotene supplements are harmful to those at risk for lung cancer. People who took beta-carotene dietary supplements, while enrolled in the trial, continued to have increased rates of lung cancer 6 years after the trial was stopped early and the supplements discontinued. These results reinforce earlier findings from this study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Genetics

An international consortium of researchers has found a major lung cancer susceptibility region on a segment of chromosome 6 that likely contains a gene(s) that increases lung cancer risk. Non-carriers of the gene(s) experienced increased risk for lung cancer in proportion to the amount they smoked. In carriers, any amount of smoking increased risk. Researchers next seek to specifically identify the potential susceptibility gene(s), which may one day enable screening for increased lung cancer risk.

Investigators from the University of Pittsburgh Cancer Center used high throughput SNP analysis to demonstrate an increased risk of lung cancer in people with polymorphisms in genes for DNA repair and metabolite elimination. In 2003, these investigators reported that SNP-related variability in estrogen metabolism was associated with an increased risk for lung cancer.

NCI scientists recently found cigarette smoking to increase the prevalence and spectrum of tumor suppressor gene p53 mutations in breast tumors, suggesting a genotoxic effect of smoking in breast tissue. This study also has important implications because breast tumors having p53 mutations exhibit more aggressive growth and are associated with poor prognosis, and smokers are more than twice as likely to have p53 mutation-positive breast cancer.

Prevention and Control

Tobacco Use and Addiction

Recent analysis of prospective data from the National Collaborative Perinatal Project shows that both male and female offspring of mothers who reported smoking a pack or more of cigarettes during their pregnancy were significantly more likely to be susceptible to tobacco-dependence than offspring of mothers who reported never smoking during pregnancy.

Results from a longitudinal study surveying nearly 5,000 rural middle school children about a variety of behaviors suggest that viewing smoking in movies strongly predicts whether or not adolescents initiate smoking, and the effect increases significantly with greater movie-smoking exposure. Fully 52 percent of smoking initiation among adolescents in the study could be attributed to this risk factor.

TTURC researchers developed the 68-question Wisconsin Inventory of Smoking Dependence Motives (WSDM-68) questionnaire to identify motivations for smoking. Researchers found that individuals who smoked automatically, to enhance mental activity, to alleviate distress, or because they were in a smoking environment, were most likely to relapse while quitting.

Tobacco Cessation

TOBACCO CONTROL INTERVENTIONS

The NCI and the American Cancer Society-supported American Stop Smoking Intervention Study (ASSIST) (*http://cancer.gov/newscenter/pressreleases/ASSISTQandA*) provided the first evidence that investing in state tobacco control programs can reduce smoking rates. Interventions were developed and implemented in 17 states by networks of state and local tobacco control coalitions. Researchers estimate that if all 50 states and the District of Columbia had implemented ASSIST policies, approximately 1,213,000 fewer people would smoke.

The NCI and the Centers for Disease Control and Prevention (CDC) have launched a National Network of Tobacco Cessation Quitlines to connect callers with local programs that deliver information, advice, support, and referrals to tobacco users who want to quit. An easy-to-remember, toll-free telephone number, 1-800-QUIT-NOW, serves as a single access point to state-based cessation services. In addition, the NCI-supported website (*www.smokefree.gov)* offers smoking cessation advice and downloadable information.

A recent survey of state employers shows that only 29 of 45 states surveyed require smoking cessation treatment to be included in health insurance plans of state employees. Only 17 states provided the complete range of coverage for smoking cessation recommended by the U.S. Public Health Service. This research shows that states are lagging in adopting this promising avenue for reducing smoking rates among their employees.

According to a recent TTURC audit of the Wisconsin Medicaid medical records, physicians asked only 55 percent of adolescent patients about their smoking status during a 2-year period. The older the patient, the more likely the physicians were to record smoking status. Pregnant teenagers were also more likely to be questioned about smoking. Previous studies based on physician self report may have overestimated smoking interventions with adolescents.

NCI's Smoking and Tobacco Control Monographs (*http://cancercontrol.cancer.gov/tcrb/monographs/*) have provided timely information about emerging public health issues in smoking and tobacco control and accelerated its dissemination to the scientific and public policy communities. In 2003, the NCI released the final monograph in the original series, Those Who Continue to Smoke: Is Achieving Abstinence Harder and Do We Need to Change Our Interventions?

In May 2002, the NCI-supported National Partnership to Help Pregnant Smokers Quit (*http://www.helppregnantsmokersquit.org/*) published an action plan to achieve the Healthy People 2010 goal of decreasing the percentage of pregnant women who smoke to less than 2 percent. In September 2002, a collaboration of ten public and private organizations released A National Blueprint for Disseminating and Implementing Evidenced-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation. Preparing for Action: Implementing the Youth and Adult Tobacco-Use Cessation National Blueprints was released in July 2003 (*http://ctcinfo.org/resources/blueprints.asp*).

Smoking-related NCI publications available to the public include: *Clearing the Air*, a manual designed to help smokers quit; *Clear Horizons*, a quitting guide for those older than 50; and the Spanish-language guide on smoking cessation, *Guia para Dejar de Fumar* (*http://www.smokefree.gov/info.html*).

Cessation Treatments

Early results from a TTURC-sponsored study of selegiline (an MAO-B inhibitor that inhibits dopamine metabolism) as a treatment for tobacco addiction suggests that selegiline was safe and superior to placebo for smoking cessation. Further research will show whether this drug can improve smokers' ability to quit.

Genetics

TTURC investigators discovered that the CYP2B6 gene, which causes reduced nicotine metabolism in the brain, may influence the effectiveness of buproprion treatment for smoking cessation. In the study, smokers received placebo or bupropion, plus behavioral group counseling. Smokers who had variants of CYP2B6 were less successful in quitting smoking. Buprobrion seemed to help overcome this genetic effect in women smokers by decreasing withdrawal symptoms.

A smoking cessation study revealed that smokers with a specific combination of genetic variants of the SLC6A3 dopamine transport gene and the DRD2 dopamine receptor gene had significantly higher abstinence rates and a longer time before relapse than smokers who did not carrying these variants. This study provides the first evidence that genes altering dopamine function may influence smoking cessation and relapse during treatment. Other researchers reported that smokers with a particular variant of the dopamine receptor gene are more likely to experience a greater sense of food reward, leading to weight gain after quitting smoking. Bupropion helped to prevent post-smoking cessation weight gain in these individuals.

Chemoprevention

The NCI supports preclinical studies focused on identifying and prioritizing agents that prevent cancers in tobacco-susceptible organ systems. Clinical researchers are evaluating the efficacy of chemopreventive agents in specific cohorts of former smokers.

Early Detection, Diagnosis, and Prognosis

Imaging

Researchers have completed enrollment of 50,000 current smokers and former smokers into the ACRIN and NCI-supported National Lung Screening Trial (NLST; *http://www.nci.nih.gov/nlst*). Approximately half of the participants are women; about 4 percent are racial/ethnic minorities. This 8-year, multisite study will determine whether lung cancer screening using low-dose spiral computed tomography in high-risk populations reduces mortality from this disease compared with standard x-ray screening. NLST scientists will also assess the stage of tumors when first detected, quality-of-life and psychological issues for people who test positive for lung cancer, economic consequences, and other potential differences between the two screening methods.

In other NCI-supported work, researchers are investigating spiral computer tomography (CT) with computer-aided diagnosis for detection of small lung nodules, and positron emission tomography (PET) for prognostic measurement of treatment-related tumor volume changes in non-small cell lung cancer (NSCLC) patients. A recent NCI-supported meta-analysis has shown PET scans to be superior to CT scans for detecting NCSLC mediastinal lymph node metastasis.

Molecular Signatures

Researchers supported by the NCI Director's Challenge program have identified a molecular signature that distinguishes early lung cancers that are likely to recur quickly, from those with a more favorable prognosis. A large, multisite confirmatory study is now underway.

Treatment

Chemotherapy

Findings of two large clinical trials, one NCI funded, show conclusively that post-surgical chemotherapy for early-stage NSCLC significantly improves overall survival. In the NCI-supported trial, the risk of death from lung cancer was reduced by 49 percent in patients who received chemotherapy with carboplatin and paclitaxel (Taxol®). The second study showed improved survival in patients receiving cisplatin and vinorelbine. Choice of chemotherapy,

length of administration, and role of post-surgical radiation therapy need to be further defined in clinical trials.

In the largest Phase III trial of second-line therapy for NSCLC patients, pemetrexed (Alimta®) was found to be equivalent to docetaxel (Taxotere®), the standard agent for second-line therapy, in terms of response. However, pemetrexed was much better tolerated by patients and has since been approved by the FDA for NSCLC therapy.

Molecularly Targeted Therapy

The FDA has approved two epidermal growth factor receptor (EGFR) inhibitors, gefitinib (Iriessa®) and erlotinib (Tarceva®), for use in NSCLC patients. About 10 percent of advanced-stage NSCLC patients respond dramatically to these targeted agents, while the other 90 percent do not respond as well. NCI-supported researchers recently discovered that a subgroup of NSCLC patients have EGFR mutations, shown in parallel *in vitro* studies to correlate with clinical responsiveness to erlotinib and gefitinib. This research suggests that mutational analysis of EGFR in tumors should help identify patients who are likely to respond to these agents and paves the way for genetic identification of patients who may respond to other molecularly targeted drugs.

Immunotherapy

In partnership with Cell Genesys, the NCI is sponsoring one of two Phase II trials of the patient-specific vaccine, GVAX® against NSCLC. This vaccine, which uses genetically modified, irradiated cells from individual patient's tumors, caused only low-level toxicities in phase I studies, and the majority of patients showed at least some immune response, with some patients stabilized for up to 3 years after treatment. The role of immunotherapy in lung cancer remains to be determined.

Health Disparities

The National Conference on Tobacco and Health Disparities, held in December 2002, was the first scientific gathering to convene researchers and practitioners with the purpose of developing a research agenda to eliminate tobacco-related disparities. The summary report (*http://dccps.nci.nih.gov/TCRB/eliminating_tobacco_hd.pdf*) presents key recommendations to provide direction for research action, processes, and communication needed to build the evidence base for reducing tobacco use and the disproportionate burden of tobacco use and its consequences.

The Tobacco and Health Disparities Research Network, supported by the NCI, Pennsylvania State University, and the American Legacy Foundation conducts interdisciplinary research to understand tobacco-related health disparities, translate scientific knowledge into practice, and inform public policy. This is the only national research network on tobacco and health disparities and offers a unique forum for stimulating scientific inquiry, promoting scientific collaborations, and evaluating the scientific evidence of research. One of the first major questions to be addressed is focused on the effects of tobacco control policy and women of low socioeconomic status.

Colorectal Cancer

It is estimated that 73,470 women in the United States will be diagnosed with cancer of the colon or rectum in 2005; an estimated 2,750 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women. African American women have the highest incidence and mortality rates, followed by white women. Modest decreases in colorectal cancer incidence and mortality over the past decade have been largely attributed to the detection and removal of precancerous polyps, the early detection of tumors through screening, and improved treatments. However, the rate of colorectal screening remains low nationally and the potential benefit with broader utilization has yet to be achieved. Five-year survival rates are highest among Asian Pacific Islander women and lowest among Black women. Lower rates of treatment with adjuvant therapy among Black patients may contribute to differences in cancer survival.

Gastrointestinal SPOREs

The NCI supports five Gastrointestinal SPOREs, which focus research on cancers of the colon, rectum, and other digestive organs. For example, SPORE researchers are evaluating the role of COX-2 and other proteins in the development

and progression of colorectal cancer; identifying molecular markers for risk prediction and treatment prognosis; developing chemoprevention regimens; and developing chemoradiation, immune, and molecularly targeted therapies.

Risk Factors

Diet

Researchers from the Arizona Cancer Center analyzed data from 1,763 participants of three randomized colorectal cancer prevention trials. They concluded that higher blood selenium concentrations were associated with lower risk for developing recurrent colorectal adenomas. Earlier, smaller epidemiological studies have variously shown either a protective effect for selenium against colorectal cancer or no association. Other NCI-supported investigators found serum levels of a vitamin D metabolite, 25-hydroxyvitamin D [25(OH)D] to be associated with lower risk for advanced colorectal adenoma in women. Analysis of data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (*http://www3.cancer.gov/prevention/plco/*) trial showed an inverse association between dietary fiber intake, especially from grains, cereals, and fruits, and risk for distal large bowel adenomas, both advanced and non-advanced.

Exogenous Hormones

Investigators from the Women's Health Initiative (*http://www.nhlbi.nih.gov/whi/*) reported a decreased incidence of invasive colorectal cancers in postmenopausal women taking estrogen plus progestin compared to women taking a placebo, even after data were adjusted for other risk factors. However, cancers diagnosed in women in the hormone group were more advanced and showed more lymph node involvement than those diagnosed in the placebo group.

Genetics

Five hundred pairs of siblings who have had colon or rectal cancer and precancerous polyps are being recruited for the Cancer Genetics Network-sponsored Sibling Pair Colon Cancer Study (*http://biostatistics.mgh.harvard.edu/siblingpair*) for identification of genetic and environmental factors involved in colorectal cancer development. The investigations will be conducted in individuals where there is no known HNPCC or familial adenomatous polyposis (FAP) in the hope of identifying cancer genetic susceptibility regions.

Colon Cancer Family Registries

The Colon Cancer Family Registries (CFRs) (*http://epi.grants.cancer.gov/CFR/about_colon.html*) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of colon cancer.

Prevention

Celecoxib

The NCI suspended use of celecoxib, in late 2004, for all participants in the Adenoma Prevention with Celecoxib (APC) trial after analysis of an independent Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and non-fatal cardiovascular events for participants taking the drug compared to those taking a placebo. Although the drug was stopped in ongoing trials, the data on the efficacy of Celecoxib in reducing polyps will not be known until the clinical followup is completed in mid-2005. In earlier studies, Celecoxib, a selective COX-2 inhibitor, has been shown to significantly reduce polyp formation in patients with FAP, without affecting blood clotting and with fewer gastric side effects than those caused by traditional non-steroidal anti-inflammatory drugs (NSAIDS). Safety monitoring of a study similar to the FAP trial, sponsored by Pfizer, did not find an increased risk of cardiovascular events. Investigators will continue to analyze the efficacy data from the APC trial.

NSAIDS

Through two NCI-funded, randomized clinical trials, investigators confirmed earlier observational studies that daily aspirin can reduce the development of colorectal polyps. Patients at increased risk for colorectal cancer who took daily aspirin for 3 years reduced colorectal polyp development by up to 35 percent. A randomized phase II clinical trial will compare the effectiveness of three drugs in preventing colorectal cancer: two NSAIDS—aspirin and Clinoril®—and the naturally occurring bile salt, ursodiol (Actigal®). The latter drug is used to dissolve

gall stones or to treat a rare inflammatory disease of the bile ducts and has been shown to reduce levels of deoxycholic acid, a bile acid with tumor promoting properties.

Statins

The NCI will conduct a randomized clinical trial to test early findings that cholesterol-lowering statins may help prevent colorectal cancer in individuals who are at high risk for the disease. Statins, the most frequently prescribed medications in the United States, work by blocking HMG-CoA, an enzyme which the body needs to make cholesterol.

Vaccines

NCI researchers recently demonstrated that immunosuppressive, anti-inflammatory chemoprevention agents could be used effectively in combination with immune-stimulating prevention vaccines. These scientists tested the combined effects of celecoxib and the experimental CEA prevention vaccine in a mouse model for human FAP. Mice receiving celecoxib plus the vaccine developed fewer tumors than mice receiving either intervention alone. The combination therapy resulted in 95 percent less tumor development and significantly improved overall long-term survival compared to the untreated group.

Proteomics

In 2003, NCI scientists reported on the use of proteomic analysis to predict patient response to a cancer chemoprevention drug. Researchers, who analyzed serum samples from 55 participants in a clinical prevention trial of the drug celecoxib, identified a protein pattern that differed between patients who benefited from celecoxib from those who did not. Further research is needed before patients' responses to specific chemopreventive drugs can be reliably predicted. NCI's Colorectal Cancer PRG emphasized the need for new technologies, such as this, to improve colorectal cancer prevention, detection, and treatment.

Early Detection, Diagnosis, and Prognosis

Colorectal Cancer Screening

The NCI's Colorectal Cancer Screening initiative supports exploratory and developmental research aimed at improving the delivery, use, and short-term outcomes of colorectal cancer screening in primary care practice. This initiative also supports efforts by primary care practices to improve their capacity to collect patient, provider, practice, and clinical data and to conduct interventions that focus on increasing colorectal cancer screening.

Recent analysis of results from the National Survey of Colorectal Cancer Screening Practices (*http://healthservices.cancer.gov/surveys/colorectal/*) identified underutilized screening techniques and procedures and showed that, although colorectal screening awareness is high among primary care physicians, there are knowledge gaps about the appropriate timing and frequency of screening. Results from another NCI-sponsored survey suggest that physicians may be performing surveillance colonoscopies at frequencies higher than those recommended by evidence-based medical guidelines. For patients considered to be at low risk for colon cancer, the cumulative chance of complications from colonoscopy along with access issues, could offset the benefits of the test.

NCI researchers found that physician-oriented reminder feedback and educational intervention significantly increased performance rates of complete diagnostic evaluation or CDE (i.e., colonoscopy, or combined flexible sigmoidoscopy plus barium enema X-ray) after an abnormal screening fecal occult blood test (FOBT).

PLCO Trial Results

Researchers from the PLCO Cancer Screening Trial have reported that 3 years following a negative sigmoidoscopy, 13.9 percent of 9,317 trial participants had a polyp growth, 2.3 percent had nonadvanced adenomas, and 0.8 percent had advanced adenomas or cancer. These results provide new insight into the appropriate screening intervals for colorectal cancer after a negative exam.

DNA Screening

NCI scientists are developing the multi-target assay panel (MTAP), a new, noninvasive method for colorectal cancer screening. The MTAP detects the presence of 21 specific DNA mutations known to be present in colorectal cancer, as well as changes in DNA structure. In early testing, researchers found the sensitivity and specificity of the MTAP to compare favorably with the FOBT.

The MTAP correctly identified over 60 percent of patients known to have colorectal cancer versus 40 percent detected correctly using the FOBT. The MTAP improperly diagnosed about 4 percent of control group patients as having cancer versus a 6 percent false-positive rate for the FOBT.

Treatment

Surgery

Most patients diagnosed with colorectal cancer are treated surgically, with adjuvant chemo- and/or radiation therapy. In a large, NCI-sponsored, randomized clinical trial, patients with colon cancer experienced similar rates of recurrence whether they were treated with laparoscopically assisted surgery or open colectomy. The trial's investigators concluded that laparoscopically assisted surgery is an acceptable, less invasive, alternative for many patients with colon cancer. Another NCI study of over 7,000 rectal cancer patients has revealed that rates for permanent colostomy and post-operative mortality were lower, and overall survival higher, for patients undergoing surgery at high- compared to low-volume hospitals. Researchers recommend further study to identify processes of care that contribute to these differences in outcomes.

Chemotherapy

NCI researchers recently updated findings on the effectiveness of the FOLFOX regimen (oxaliplatin, 5-fluorouracil, and leucovorin) in patients with metastatic colorectal cancer, reporting a median survival of 19.5 months compared to 14 to 15 months for patients treated with ILF (irinotecan, folinic acid, and infusional 5-fluorouracil). A group of non-NCI-funded researchers showed that oxaliplatin administered with 5-fluorouracil and leucovorin was also superior to ILF as post-surgery adjuvant for patients with stage II and stage III colorectal cancer.

Immune Therapy

The NCI is sponsoring a phase III clinical trial testing therapy with the angiogenesis-targeting, anti-VEGF monoclonal antibody bevacizumab (Avastin™), in patients who have received prior chemotherapy. Partially NCI-funded Genentech trials have shown that, in patients who had not yet been treated with chemotherapy, addition of bevacizumab to standard chemotherapy (fluorouracil, leucovorin, and irinotecan) improved survival (14 versus 19 months), response rate, and time to progression.

Research supported by the NCI and others has led to the FDA approval, in February 2004, of the monoclonal antibody, cetuximab (Erbitux®), for treatment of advanced colorectal cancer in combination with irinotecan chemotherapy. Cetuximab, the first monoclonal antibody approved for colorectal cancer treatment, has not been shown to improve overall survival, but was shown to shrink tumors and slow tumor growth in some patients.

AIDS-associated Malignancies

AIDS and HIV infection continue to be major public health concerns. From 1981 to 2001, 929,985 cases of AIDS were reported to the CDC. In 2003, 43,171 new cases of AIDS were reported to the CDC; more than one-third were in women. There were also 33,301 new cases of HIV infection reported; however, this is likely an underestimate since not all states report new cases. In 2003, 28 percent of HIV/AIDS cases were in women and 69 percent of those were in Black women. Heterosexual transmission of HIV increased from 3 percent in 1985 to almost 31 percent in 2003. About 70 percent of HIV-positive women were infected by this route in 2003. While the numbers of deaths per year in the United States due to AIDS has decreased in the era of highly active antiretroviral therapy (HAART), the numbers of persons living with the disease has increased. Approximately 580,500 persons are currently living with HIV infection or AIDS in the United States. Of those, 141,048 adult and adolescent women are living with AIDS, mostly minority women, and 49,226 are living with HIV infection.

The longer life expectancy of HIV-positive people with access to HAART, who are living with partially restored immune function, may increase the cumulative risk of developing both AIDS-defining and non-defining cancers. The ultimate risk of such patients developing cancers more commonly associated with aging or those with longer latency, such as hepatocellular carcinoma, is not yet known. The AIDS-defining malignancies are non-Hodgkin's

lymphoma (NHL), cervical cancer, anal cancer, and Kaposi's sarcoma (KS). Although KS is extremely rare among women, NHL currently ranks sixth in overall female cancer incidence and mortality. In addition, there is an increased incidence of NHL in women from the pre-HAART to HAART period. The risk of cervical neoplasia is five times higher in women with HIV infection than in HIV-negative women, due to a higher prevalence and persistence of oncogenic HPV infection. The prognosis for cervical cancer is also poorer for HIV-positive than for HIV-negative women. Women infected with HIV and HPV also have a 6.8-fold greater risk of invasive anal cancer than HIV-negative, HPV-positive women.

Lymphoma SPORE

The NCI lymphoma SPORE, located at the John Hopkins University, (*http://spores.nci.nih.gov/current/lymphoma/lymphoma_docs/lym-ambinder.html*) is investigating the molecular epidemiology of AIDS-related NHL (AIDS-NHL). These researchers seek to identify immune-related molecular changes that precede AIDS-NHL development and molecular markers for AIDS-NHL risk assessment, as well as treatment strategies for high-risk individuals.

Women's Interagency HIV Study (WIHS)

Since 1995, the NCI has co-funded the WIHS to support malignancy studies in this NIAID/NICHD/NIDA initiative (*https://statepiaps.jhsph.edu/wihs*), the largest U.S. study of HIV infection in women. HIV-infected women have increased incidence rates for KS (more than 200-fold), NHL (23-fold), and lung cancer (tenfold) when compared to SEER rates. No significant increases have been detected among HIV-infected and high-risk uninfected WIHS women for lung cancer after adjusting for cigarette smoking. Only one confirmed case of invasive cervical cancer has occurred to date in an HIV-infected woman participating in WHIS, most likely detected due to the intensive cytologic surveillance conducted in this study. Other studies have reported excess of invasive cervical cancer in HIV-positive women. Despite concerns to the contrary, no increased risk of breast cancer or unusual types of breast tumors have been detected in over 5,000 women in followup. HIV-infected women who initiated HART experienced significant reductions in overall cancer risks. However, NHL incidence remains significantly higher in this population compared to the HIV-uninfected U.S. population. WIHS women have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

Risk

Immune Suppression

NCI researchers linked records from AIDS and cancer registries in 11 U.S. regions to evaluate the relationship between cancer risk and AIDS-related immunosuppression as measured by CD4 count at AIDS onset. Based on the records of 82,217 adults, risks for KS and NHL were inversely related to CD4 count. Risks for other cancers, including cervical cancer, were unrelated to CD4 counts.

Treatment

DA-EPOCH

In 2003, NCI researchers reported development of the dose-adjusted EPOCH (DA-EPOCH) treatment regimen for patients with AIDS-related lymphoma (ARL). DA-EPOCH substantially improved survival for ARL patients in comparison with then standard CHOP therapy. Patients treated with DA-EPOCH were given low, individualized drug dosages, thereby reducing drug resistance and toxicity. Importantly, antiretroviral therapy was safely suspended during DA-EPOCH therapy, boosting treatment effectiveness.

Developing Novel Therapies

NCI researchers are searching for more effective AIDS therapies that will reduce the incidence of AIDS-related malignancies. Investigators recently discovered characteristic differences in gene expression patterns among cells harboring latent HIV, those infected with replicating virus, and uninfected cells. They identified several genes that may provide targets for new treatment strategies that force latent virus to replicate, making the virus more vulnerable to anti-retroviral therapy. NCI researchers are also investigating novel treatments for AIDS malignancies, including potential anti-angiogenesis therapies for treating KS.

AIDS Malignancy Program (AMP)

The NCI developed the multicomponent AMP (*http://cancer.gov/dctd/aids*) to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients, with the goal of developing more effective treatment regimens. The AMP includes the AIDS-Associated Malignancies Clinical Trials Consortium (AMC) (*http://www.amc.uab.edu*) and the AIDS and Cancer Specimen Resource (ACSR, *http://acsr.ucsf.edu*). The ACSR contains or provides access to over 100,000 specimens and associated clinical data collected from cohort studies, clinical trials, and other research. The AMC unites 15 main member sites that conduct innovative treatment trials for AIDS-associated malignancies. A recent phase III AMC clinical trial found that improvements in tumor response associated with addition of rituximab to CHOP chemotherapy in patients with AIDS lymphoma may be offset by an increase in deaths from infections, particularly in individuals with low CD4 lymphocyte counts.

Centers for AIDS Research (CFAR)

The CFAR (*http://www.niaid.nih.gov/research/cfar*), a program co-funded by seven NIH institutes including the NCI, provides administrative and shared research support to synergistically enhance and coordinate high quality AIDS research projects, both nationally and internationally. There are 20 CFARs located at academic and research institutions throughout the United States Core facilities provide expertise, resources, and services not readily obtained through more traditional funding mechanisms. CFAR funding in 2005 will include awards to elucidate the natural history and pathobiology of HIV-related malignancies in diverse populations in men, women, and children, and to explain the role of sex and gender in AIDS therapy and prevention through collaborative studies in women and girls.

HIV and AIDS Malignancy Branch

The NCI's intramural HIV and AIDS Malignancy Branch (*http://www3.cancer.gov/mab/hnc7z27.htm* conducts translational research on HIV infection and AIDS-related malignancies in children and adults. Investigators engage in basic laboratory research, preclinical studies, and clinical trials aimed at developing novel therapies for AIDS and AIDS-related malignancies and at understanding the effects of these therapies on disease pathogenesis.

Training

AIDS International Training and Research Program (AITRP)

The NCI is a co-sponsor of the AITRP (*http://www.fic.nih.gov/programs/aitrp/aitrp.html*), which supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries.

Initiatives

Request for Application (RFAs)

- **Breast Cancer and the Environment Research Centers**
  The NCI joins the NIEHS in an initiative to create a network of research centers in which multidisciplinary teams of scientists, clinicians, and breast cancer advocates collaboratively focus on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. The centers will work collaboratively on two projects; Defining the Effects of Environmental Exposures on the Molecular Architecture of the Mammary Gland over the Lifespan, and Environmental and Genetic Determinants of Puberty. (RFA-ES-03-001)

- **Mouse Models of Human Cancers Consortium (MMHCC)**
  The activities of the MMHCC include fresh approaches to mouse genetic engineering and phenotyping, significantly advancing the field and stimulating interest in derivation and application of mouse cancer models to cancer research. The intent is to foster research investigations, technological innovation, and extensive collaboration that cannot be pursued with traditional grant support. (RFA-CA-04-002)

- **Long-term Cancer Survivors: Research Initiatives**
  The goal of this RFA is to promote and support research that will lead to the

decrease in physiologic and psychosocial morbidity and mortality associated with long-term (more than 5 years) survival from cancer. (RFA-CA-04-003)

- **Early Detection Research Network**
  The national Early Detection Research Network (EDRN) is responsible for the development, evaluation, and validation of new or existing biomarkers for earlier cancer detection and risk assessment. The intent of these RFAs is to continue to foster research investigations, technological innovation, and collaboration to accelerate the development of biomarkers and tools that have the potential of moving rapidly to phase II and phase III. (RFAs CA-04-006 , CA-05-005, CA-05-009, CA-05-023)

- **Community Clinical Oncology Program (CCOP)**
  The re-issuance of this RFA seeks to build on the strength and success of the network over the past 20 years by continuing to support community participation in cancer treatment, prevention, and control clinical trials through research bases (NCI-supported clinical cooperative groups and Cancer Centers); expanding and strengthening the cancer prevention and control research effort; utilizing the CCOP network for conducting NCI-assisted cancer prevention and control research; and evaluating CCOP performance and impact in the community. (RFA-CA-04-008, CA-05-014)

- **Understanding Mechanisms of Physical Activity and Behavior Change**
  The purpose of this RFA is to increase the knowledge base necessary to develop effective physical activity interventions in children, adolescents, adults, and older adults. Studies that consider the psychosocial, environmental, and physiological factors that influence the mechanisms of physical activity behavior change are of interest, and the physiological and psychosocial influences affected by disease status are of particular interest. This RFA is co-sponsored by the NCI, the NIDDK, the OBSSR, the ODP, and the ORWH. (RFA-CA-04-009)

- **Small Animal Imaging Resource Programs**
  These programs will support: 1) shared imaging research resources to be used by cancer investigators, 2) research related to small animal imaging technology, and 3) training of both professional and technical support personnel interested in the science and techniques of small animal imaging. (RFA-CA-04-011)

- **Transdisciplinary Tobacco Use Research Centers**
  This re-issued RFA reflects recognition of the public health impact of tobacco use and the scientific need for integrative transdisciplinary research across the full spectrum of basic and applied research on tobacco use and control. Collaborative research across disciplinary boundaries permits scientific exploration of the complex and interactive determinants of tobacco use. This RFA is co-sponsored by the NCI, the NIDA, and the NIAAA. (RFA-CA-04-012)

- **Integrative Cancer Biology Program**
  This initiative is designed to foster the emergence of the new field of systems biology focused on the analysis of cancer as a complex biological disease. The initiative will support the development of reliably predictive *in silico* or computational models of cancer initiation and progression that can ultimately lead to the development of improved cancer interventions. It will enable the formation of teams of researchers from a spectrum of fields, including biology, imaging, engineering, technology, bioinformatics, and computational modeling, who can focus on understanding and modeling some aspect of the complexity of cancer. (RFA-CA-04-013)

- **Strategic Partnering to Evaluate Cancer Signatures**
  The purpose of this initiative is to build on recent demonstrations that molecular signatures correlate with important clinical parameters in cancer. The NCI invites investigators to form strategic partnerships that will bring together the multidisciplinary expertise and resources needed to determine

how the information derived from comprehensive molecular analyses can be used to improve patient care and, ultimately, patient outcomes. (RFA-CA-04-015)

- **Transdisciplinary Research on Energetics and Cancer**
  These centers will involve scientists from multiple disciplines and will encompass projects spanning the biology and genetics of behavioral, sociocultural, and environmental influences on nutrition, physical activity, weight, energy balance, and energetics. (RFA-CA-05-010)

- **Community Networks to Reduce Cancer Health Disparities (CNP)**
  The purpose of the CNP is to reduce cancer health disparities by conducting community-based participatory education, training, and research among racial/ethnic minorities and underserved populations. The overall goals of this program are to significantly improve access to, and utilization of, beneficial cancer interventions in communities with cancer health disparities, thereby reducing these disparities. (RFA-CA-05-012)

- **Reducing Barriers in Symptom Management and Palliative Care**
  This RFA will support research directed at developing and testing interventions to reduce or overcome barriers to the delivery of appropriate symptom management and palliative care, thereby decreasing the suffering and improving the health and quality of life of persons living with cancer. This RFA is co-sponsored by the NCI, the NINR, and the ORWH. (RFA-CA-05-013)

- **Minority-based Clinical Oncology Program**
  The re-issuance of this RFA is intended to provide support to expand clinical research in minority community settings; bring state-of-the-art treatment and cancer prevention and control research to minority individuals in their communities; increase involvement of primary healthcare providers and specialists in prevention and control studies; establish an operational base for extending prevention and control and reducing cancer incidence, morbidity, and mortality in minority populations; and examine issues in minority-based CCOP performance. (RFA-CA-05-015)

- **Patient Navigation Research Program**
  The purpose of the Patient Navigation Research Program is to develop interventions to reduce the time to delivery of standard cancer care services—non-cancer resolution or cancer diagnosis and treatment after identifying an abnormal finding from a cancer detection procedure. (RFA-CA-05-019)

- **Planning Grant for Minority Institution/Cancer Center Collaboration (P20)**
  The objective of this initiative is to help researchers and faculty in Minority Serving Institutions (MSIs), in collaboration with the researchers and faculty of NCI-designated Cancer Centers (or other institutions with highly organized, integrated research efforts focused on cancer), plan and initiate focused cancer research, cancer research training, and career development or cancer research education and outreach collaborations that will lead to the submission of specific grant applications traditionally supported by the NCI or other equivalent funding agencies. (RFA-CA-05-020)

- **Comprehensive Minority/Institution/Cancer Center Partnership (U54)**
  This initiative supports cooperative agreements for the implementation of Comprehensive Minority Institution/Cancer Center Partnerships between MSIs and NCI-designated Cancer Centers (or groups of Centers). The purpose of this grant is to provide opportunities for intensive collaborations among MSIs and the Cancer Centers in order to develop stronger national cancer programs aimed at understanding the reasons behind the significant cancer disparities and impact on minority populations. (RFA-CA-05-021)

- **Cooperative Planning Grant for Comprehensive Minority Institution/ Cancer Center (MSIs) Partnership**
  Partners in these U54 programs are expected to: 1) build and stabilize the independent competitive cancer research capacity at the MSIs; 2) improve the effectiveness of the NCI-designated Cancer Centers in conducting activities specifically designed to address the cancer disparities in underserved racial and ethnic minority populations and among the socioeconomically disadvantaged; 3) create stable, long-term collaborative relationships between MSIs and Cancer Centers in all areas of cancer research, training, and education; and 4) export successful approaches and new models to other MSIs and NCI-designated Cancer Centers, as well as other key networks supported by the NCI. (RFA-CA-05-022)

Program Announcements (PAs)

- **Exploratory Studies in Cancer Detection, Diagnosis, and Prediction**
  This initiative promotes the initial evaluation of molecular or cellular characteristics in human specimens and/or the development of assays that may result in important advances in the detection, diagnosis, and treatment of cancers. (PA-03-003)
- **Studies of the Economics of Cancer Prevention, Screening, and Care**
  The goal of this PA, in partnership with the AHRQ, is to generate new economic knowledge that will promote the optimal design of cancer prevention and control trial studies and interventions and will facilitate the formulation of effective health care policy related to cancer prevention and control. (PA-04-012)
- **Exploratory Grants for Behavioral Research in Cancer Control**
  This PA invites research grant applications from interested investigators to conduct developmental and formative behavioral research in cancer prevention and control through a program of exploratory investigator-initiated R21 grants. (PA-04-034)
- **Clinical Cancer Therapy and Prevention Research**
  The overall aims of this renewed PA are twofold: 1) to stimulate development of innovative therapeutic/preventive clinical trials with or without laboratory correlative studies, and 2) to support innovative correlative laboratory studies linked to therapeutic/preventive clinical trials. (PA-04-046)
- **Developmental Projects in Complementary Approaches to Cancer Care**
  The purpose of this PA is to encourage and support the development of basic and clinical complementary cancer research and to provide the basis for more extended research projects by establishing the methodological feasibility, strengthening the scientific rationale for these projects, and collecting preliminary data. This PA is co-sponsored by the NCI, the NINR, the NIDCR, and the NCCAM. (PA-04-053)
- **Novel Technologies for *In Vivo* Imaging**
  This PA, co-sponsored by the NCI, the NIEHS, the NIDDK, and the NINDS, supports applications for the development and delivery of novel image acquisition or enhancement technology and methods for biomedical imaging and image-guided interventions and therapy. Applicants may incorporate limited pilot or clinical feasibility evaluations using preclinical models or clinical studies. (PA-04-094, PA-04-095)
- **Diet, Epigenetic Factors, and Cancer Prevention**
  The objective of this PA is to encourage collaboration between nutrition and epigenetic experts to study bioactive food components with cancer preventative properties and to examine key epigenetic events in cancer processes (i.e., carcinogen metabolism, cell division, differentiation, apoptosis) so that investigators can begin to establish linkages between epigenetics, methylation pattern, and tumor incidence/ behavior. (PA-04-099)

- **Phased Application Awards in Cancer Prognosis and Prediction**
  This PA invites applications for research projects to evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy. This research will provide tools to improve clinical decision-making in the care of cancer patients. This PA provides support for a first phase (R21) for technical development and a second phase (R33) for application and evaluation of clinical utility. (PA-04-102)

- **Testing Tobacco Products Promoted to Reduce Harm**
  The purpose of this PA, co-sponsored by the NCI and the NIDA, is to stimulate multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless, through the interplay of basic, biological, and behavioral research, surveillance, and epidemiology. (PA-04-103)

- **Research on Malignancies in AIDS and Acquired Immune Suppression**
  This PA is co-sponsored by the NCI and the NIDCR. The PA's purpose is to stimulate research that will improve our understanding of the biological basis of development and progression of cancer in the context of HIV infection and AIDS, or acquired immune suppression not associated with HIV infection, such as organ transplantation. (PA-04-157)

- **The Effect of Racial and Ethnic Discrimination/Bias on Healthcare Delivery**
  The purposes of this PA are: 1) to improve the measurement of racial/ethnic discrimination in healthcare delivery systems through improved instrumentation, data collection, and statistical/analytical techniques; 2) to enhance understanding of the influence of racial/ethnic discrimination in healthcare delivery and its association with disparities in disease incidence, treatment, and outcomes among disadvantaged racial/ethnic minority groups; and 3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination on healthcare delivery systems in the United States. This PA is co-sponsored by the NCI, the NIDDK, the OBSSR, the NHLBI, the NIBIB, and the NIDA. (PA-05-006)

- **Research on the Economics of Diet, Activity, and Energy Balance**
  The major focus of this PA is to solicit projects that enhance the state-of-the-science on the causes of obesity and to inform federal decisionmaking on effective public health interventions for reducing the rate of obesity in the United States. Research strategies that nest economic analysis within a broader interdisciplinary context of other social and behavioral sciences, as well as the epidemiological, biostatistical, medical, and biological disciplines relevant to public health policy, are especially encouraged. This PA is co-sponsored by the NCI, the NIDDK, the NIBIB, the NIA, and the OBSSR. (PA-05-009)

- **Decisionmaking in Health: Behavior Maintenance**
  The purpose of this initiative, co-sponsored by the NCI, the NIDA, and the NIAAA, is to invite applications for research projects that will expand our knowledge of basic decisionmaking processes underlying initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases, such as cardiovascular disease, diabetes, and addiction. (PA-05-016)

- **Decision Making in Cancer: Single-event Decisions**
  The purpose of this PA is to invite applications for research projects that will enhance understanding of human decision-making processes so that individuals can make more informed and satisfying choices regarding their health related to cancer prevention, detection, treatment, survivorship, or end-of-life care. (PA-05-0917)

- **Social and Cultural Dimensions of Health**
  The ultimate goal of this PA is to encourage the development of health research that integrates knowledge from the biomedical and social sciences by: 1) elucidating basic social and cultural constructs and processes used in health research; 2) clarifying social and cultural factors in the etiology and consequences of health and illness; 3) linking basic research to practice for improving prevention, treatment, health services, and dissemination; and 4) exploring ethical issues in social and cultural research related to health. This PA is co-sponsored by the OBSSR, the NCI, the NCCAM, the NHLBI, the NICHD, the NIDCR, the NIDDK, the NIEHS, the NIMH, the NINR, the NIA, the NIAAA, the NIAMS, the NIDA, and the NIDCD. (PA-05-029)

- **Specialized Programs of Research Excellence (SPOREs) in Human Cancer for the Year 2004**
  A SPORE should support a mix of basic and clinical researchers whose formal interactive and collaborative research efforts will result in new approaches for early detection, diagnosis, therapy, prevention, and control of human cancer. SPOREs are expected not only to conduct a wide spectrum of research activities, but also to contribute significantly to the development of specialized research resources (or cores), improved research model systems, and collaborative research projects with other institutions. (PAR-03-158)

- **Cancer Prevention Research Small Grant Program**
  The Small Grants Program is designed to aid and facilitate the growth of a nationwide cohort of scientists with a high level of research expertise in cancer prevention research. (PAR-04-147)

- **Small Grants for Behavioral Research in Cancer Control**
  Studies funded by this initiative may contribute to the design, implementation, or evaluation of intervention programs, descriptive baseline surveys, testing, modification, and validation of surveys or program materials for use in the proposed population groups, testing of recruitment, intervention, or compliance procedures for participants, etc. (PAR-04-020)

- **Colorectal Cancer Screening in Primary Care Practice**
  The objective of this PA, in partnership with the AHRQ, is to encourage health services, social and behavioral, and outcomes researchers to develop innovative research projects to increase the knowledge base for enhanced translation of effective colorectal cancer screening techniques into community practice. (PAR-04-036)

- ***In Vivo* Cellular and Molecular Imaging Centers (ICMICs)**
  This initiative, for new or competing P50 Research Center Grants, is designed to capitalize on the extraordinary opportunity for molecular imaging to have an impact on the diagnosis and treatment of cancer patients non-invasively and quantitatively. (PAR-04-069)

- **Quick-Trials for Novel Cancer Therapies: Exploratory Grants**
  This PA is intended to provide investigators with rapid access to support for pilot, phase I and phase II cancer clinical trials, as well as support for patient monitoring and laboratory studies linked to a cancer clinical trial. (PAR-04-155)

Conferences and Workshops

- **Emerging Topics in Breast Cancer and the Environment Research**
  Princeton, NJ; November 4-6, 2004

- **Mini-Symposium on Work and Women's Health at the International Symposium on Epidemiology in Occupational Health**
  Melbourne, Australia; October 13-15, 2004

- **Exploring Genomics in Ovarian Cancer—Division of Cancer Epidemiology and Genetics (DCEG) Seminar Series**
  Rockville, MD; September 16, 2004

- **Cancer Health Disparities Summit 2004—Special Populations Networks for Cancer Awareness Research & Training**
  Washington, DC; July 18-20, 2004
- **Workshop on Cancer Risk Prediction Models: Development, Utility, Evaluation, and Applications**
  Washington, DC; May 20-21, 2004
- **Working Together to Address the Unequal Burden of Cancer—Reaching Special Populations in the Mid South to Lessen Cancer Disparities: Sharing Innovative Ideas and Sustaining Outcomes**
  Lexington, KY; May 18-20, 2004
- **8th International Conference on Malignancies in AIDS and Other Immunodeficiencies (ICMAOI)): Basic, Epidemiologic, and Clinical Research**
  Bethesda, MD; April 29-30, 2004
- **State-of-the-Science Conference on Workplace Strategies and Interventions for Improving Health and Well Being**
  Bethesda, MD; April 13-14, 2004
- **9th Biennial Symposium on Minorities, the Medically Underserved, and Cancer**
  Washington, DC; March 24-28, 2004
- **Parenthood after Cancer: Today's Options and Tomorrow's Hopes**
  Houston, TX; March 5-7, 2004
- **Cervix Carcinogenesis in Terms of HPV Infection**
  Bethesda, MD; March 3, 2004
- **4th Congress of the International Association for Breast Cancer Research: Advances in Human Breast Cancer Research and Preclinical Models of Breast Cancer Research**
  Sacramento, CA; November 2003
- **DNA Repair, Smoking, and the Risk of Lung Cancer**
  Rockville, MD; November 13, 2003
- **Borderline Ovarian Tumors Consensus Workshop**
  Bethesda, MD; August 27-28, 2003
- **Breast Cancer Faculty Annual Retreat**
  Warrenton, VA; July 9-10, 2003
- **International Meeting on Angiogenesis in Cancer**
  Reykjavik, Iceland; June 26-28, 2003
- **Mammary Gland Biology Seminar Series**
  Bethesda, MD; Spring 2003
- **7th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic, and Clinical Research**
  Bethesda, MD; April 28-29, 2003
- **NCI Rosalind E. Franklin Award for Women in Cancer Research: An Approach to Studying Genetic Susceptibility of Lung Cancer—Division of Cancer Epidemiology and Genetics (DCEG) Seminar Series**
  Rockville, MD; March 6, 2003
- **Future Vaccines for Papilloma and AIDS Viruses**
  Bethesda, MD; February 28, 2003
- **Early Reproductive Events and Breast Cancer**
  Bethesda, MD; February 24-26, 2003
- **4th National Forum on Biomedical Imaging in Oncology**
  Bethesda, MD; February 6-7, 2003
- **Women, Tobacco, and Cancer: An Agenda for the 21st Century**
  Houston, TX; February 3-5, 2003
- **Ovarian Cancer: Insights from Gene Expression Profiling**
  Bethesda, MD; January 23, 2003

THE NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

The National Center for Complementary and Alternative Medicine (NCCAM) was established through a congressional mandate under the FY 1999 Omnibus Appropriations Bill PL105-277 signed by the President in October of 1998. The mission of the 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. CAM encompasses those health care and medical practices that are not currently an integral part of conventional medicine. The list of CAM practices and therapies changes as ones proven to be safe and effective become accepted as "mainstream" healthcare practices. NCCAM groups CAM practices within five major domains: 1) whole medical systems (i.e., traditional Chinese medicine, Naturopathic Medicine, Ayurveda); 2) mind-body medicine (i.e., meditation, biofeedback); 3) biologically based practices (i.e., herbal therapies, special diets); 4) manipulative and body-based practices (i.e., Chiropractic, massage); and 5) energy medicine (i.e., Reiki, Qi gong). NCCAM conducts and supports basic and applied (clinical) research and research training within these areas.

The 2002 National Health Interview Survey found that 62 percent of the 31,044 respondents had used some form of CAM therapy in the past year; when prayer for health reasons was excluded from the definition, over a third (36 percent) reported use of CAM in the previous 12 months. After prayer for one's own health (43 percent), the other most common forms of CAM used were natural products (18.9 percent), deep breathing exercises (11.6 percent), meditation (7.6 percent), chiropractic care (7.5 percent), yoga (5.1 percent), massage (5.0 percent), and diet-based therapies (3.5 percent). Women were more likely to use CAM than men, with the largest gender differential seen with mind–body therapies, including prayer specifically for health purposes. CAM therapies are used to treat a broad range of health conditions by both men and women, including back and neck problems, allergies, fatigue, arthritis, headaches, diabetes, and cardiovascular disease. CAM therapies for women treat a variety of conditions such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and urinary tract problems. Thus, the NCCAM's research portfolio includes investi-
gations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

Accomplishments

Menopause

In 2002, the Women's Health Initiative (WHI) found increased risk for cardiovascular disease, blood clots, and breast cancer among women receiving estrogen plus progestin to treat menopausal symptoms. Since that time, other risks have been identified with hormone therapy, shifting the risk-benefit balance away from use of hormones to treat many of the symptoms associated with menopause. A 1999 survey found that women in the United States spent $600 million on products thought to be helpful for menopause. According to longitudinal survey data from the Study of Women's Health Across the Nation (SWAN), almost 50 percent of peri- and postmenopausal women had used CAM therapies in the year prior to interview. In the wake of the WHI, aggressive marketing campaigns are encouraging the use of CAM products for menopausal symptoms, 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), paced respiration, magnet therapy, reflexology, acupuncture, and homeopathy.

The NCCAM has a strong interest in menopausal health since many women use alternative therapies to treat hot flashes and other symptoms associated with the menopausal transition. Moreover, alternatives to hormone-based therapies are needed for women with a history of breast cancer whose tumors may be hormone dependent.

Over the past 2 years, the NCCAM has developed a multi-pronged approach to improving our knowledge of CAM for the treatment of menopausal symptoms—convening workshops, producing reports,

and supporting research and research training. For example, in January 2004, the NCCAM, in collaboration with the ORWH and several other NIH ICs, convened a workshop to assess the quality of measures of hot flashes. (A summary of that workshop is available on the NCCAM website.) Critical to the evaluation of treatment efficacy is the quality of outcome measures. However, when objective measures (i.e., sternal skin conductance) are compared with self-reported measures taken under ambulatory conditions, women significantly underreport the frequency of hot flashes. In September 2004, the NCCAM, along with the NIA, the NIBIB, and the ORWH, issued a Request for Applications for SBIR applications to improve sternal skin conductance technologies to facilitate long-term data collection on hot flash frequency under ambulatory conditions. We expect to make up to five awards in FY 05.

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

In response to concerns raised about the safety of black cohosh, an herbal dietary supplement used to treat menopausal symptoms, the NCCAM and the Office of Dietary Supplements (ODS) convened a workshop in November 2004. The NCCAM and other NIH ICs participating in the workshop support clinical research on black cohosh. First and foremost is our concern for the safety of research subjects. Given ambiguity and uncertainty in the scientific literature, we wondered what additional actions, if any, the NIH needed to take to protect research participants. That workshop reviewed what is known about purported estrogenic activity of black cohosh, its effect on breast and prostate tissue, data from a murine model suggesting an increased incidence of metastatic lesions from breast to lung among animals fed black cohosh, and several cases of hepatotoxicity alleged to be connected to use of this dietary supplement. After discussing data presented at the meeting, the group concluded that there was little evidence that black cohosh had estrogenic activity and that the mouse study needed to be published and replicated. The group noted that existing surveillance systems report very few side effects. In reviewing several cases of hepatotoxicity presented at the workshop, participants found it difficult to know exactly what was taken by several cases. Nevertheless, the group concluded that patient safety is of paramount importance in clinical studies, and liver function should be carefully monitored in all clinical studies of black cohosh. The workshop report is available on the NCCAM website.

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

Ongoing clinical research on menopause targets several CAM botanical therapies, including black cohosh, red clover, soy, and other phytoestrogens, as well as the use of non-botanical treatments (e.g., therapeutic touch, macrobiotic diet) to deal with a range of symptoms, such as hot flashes, osteoporosis, and cognitive and affective problems. Examples of more clinically oriented research include

a study on the impact of phytoestrogens on cognition, affect, and atherosclerosis, and an epidemiologic study of the influence of soy consumption on menopause in Japan. The Center on Botanical Dietary Supplements for Women's Health in Chicago, supported by the ODS and the NCCAM, is completing studies on the clinical safety and efficacy of botanicals used to treat women's health with particular emphasis on therapies for menopause. Projects are preparing standardized dietary supplements, isolating active compounds for structure elucidation, and determining the mechanism of action and efficacy of several botanicals (i.e., black cohosh and red clover) used for menopausal symptoms, including hot flashes, bone turnover, and vaginal dryness. Work at another ODS/NCCAM-funded center, the Botanical Center for Age-Related Diseases in Indiana, focuses on characterizing active ingredients in botanicals. They will determine the efficacy of polyphenolic compounds in reducing risk of age-related diseases, including osteoporosis, cancer, cardiovascular disease, and neurodegeneration. Specific projects will study isoflavones and bone resorption in postmenopausal women; the effects of soy isoflavones on prostate, breast, and bone; and soy and estrogen interactions on breast and endometrium markers.

Premenstrual Syndrome and Endometriosis

Premenstrual syndrome (PMS) is a significant mood and physical disturbance that occurs during the latter half of the menstrual cycle. More than 40 percent of women of reproductive age experience PMS. Several CAM therapies are used to treat PMS, including dietary supplements, aromatherapy, guided imagery, and meditation. The NCCAM recently funded a basic research project to look at the molecular mechanisms of *Vitex agnus-castus L.* (VAC or chasteberry) in PMS. This study will evaluate the affinity of different VAC extracts for opiate receptors, as well as binding and activation of brain opiate receptors in a murine model.

Endometriosis is a progressive gynecologic disorder and a leading cause of infertility. Chronic pelvic pain often accompanies endometriosis and has important implications in the quality of life of women suffering from this disorder. The majority (70 percent) of patients with unresponsive pelvic pain have endometriosis. Research on treatment for this disorder has often focused on adult women, not adolescents. Lupron, a drug that is often used to treat women with endometriosis, is not approved for use in patients less than 16 years of age. The NCCAM recently funded a developmental center at the New England School of Acupuncture. One of the center's projects will study the effect of acupuncture on chronic pelvic pain in adolescent and young women with endometriosis.

Arthritis and Fibromyalgia

The prevalence of arthritis in the United States has been estimated to range from 15 to 18 percent, affecting approximately 40 million people. Arthritis is a disease that differentially affects women. In 1997, nearly 30 percent of arthritis sufferers queried in a national survey reported the use of CAM to treat the disease. This represents a significant increase in use in this population since 1990 (18 percent). Data from the 2002 NHIS survey found that approximately 5 percent of adults surveyed used CAM for joint pain or stiffness or arthritis or fibromyalgia, 6.6 percent used it for neck pain, and 16.8 percent used it for back pain or back problems.

The most common type of arthritis is osteoarthritis (OA), a progressive disorder that often results in significant pain and limited range of joint motion. Women aged 60 and older are nearly twice as likely as men (30 vs. 17 percent) to report a history of OA. The NCCAM is supporting a range of clinical and basic research on OA, including a brain imaging study to learn more about the mechanism of action of acupuncture. The NCCAM supports definitive clinical trials on two CAM interventions to treat symptoms associated with OA of the knee: acupuncture and glucosamine with or without chondroitin sulfate. These studies have sufficient statistical power to test for treatment effect differences by gender. The acupuncture study has been completed and the results are described below. The glucosamine study should be completed in the next year.

The Center for Alternative Medicine Research of Arthritis at the University of

Maryland Medical School has been conducting multidisciplinary research on both clinical and basic research aspects of arthritis, including safety, efficacy, and cost-effectiveness studies on acupuncture for osteoarthritis of the knee and electroacupuncture for persistent pain and inflammation. Dr. Berman and colleagues conducted the longest and largest randomized controlled phase III clinical trial of acupuncture ever conducted—570 patients with OA of the knee were randomly assigned to one of three treatment arms: acupuncture, sham acupuncture, or control (the Arthritis Foundation's self-help course). All patients continued to receive standard medical care from the primary care physicians, which included anti-inflammatory medications, non-steroidal anti-inflammatory drugs, and opioid pain relievers. The findings of the study were recently published in the *Annals of Internal Medicine*, noting that individuals receiving acupuncture had greater pain relief and improved function than individuals receiving sham acupuncture or control, thus indicating that acupuncture is indeed an effective complement to standard care.

Other relevant work conducted in another NCCAM center pertains to the safety and efficacy of several botanicals purported to have anti-inflammatory action, which could be useful in the treatment of arthritis or other chronic inflammatory diseases. That work is ongoing at the Arizona Center for Phytomedicine Research in Tucson. Scientists in the center are studying *Curcuma longa rhizome* (powdered turmeric root), *Zingiber officinale rhizome* (powdered ginger root), and the gum resin of *Boswellia serrata* (boswellia). Findings published to date indicate that boswellia does not ameliorate inflammation in a murine model and at higher doses produces hepatotoxic effects in mice. Analyses of ginger (*Zingiber officinale*) detected 20 previously unknown natural products, as well as 31 compounds previously reported as ginger constituents. Anti-inflammatory activity of silica gel chromatography fractions were tested using an *in vitro* PGE2 assay. Most of the fractions containing gingerols or gingerol derivitives showed excellent inhibition of LPS-induced PGE2 production.

In addition, the NCCAM is funding a study of the consistency of traditional Chinese medicine practitioners' diagnosis of RA and prescription of herbal formulas for women. Another study of RA in women is being conducted by intramural NCCAM scientists trying to understand the impact of systemically released inflammatory cytokines on the suppression of the GH/IGF-1 axis and the relationship of altered endocrine-immune function with endocrine, metaboic, and vascular functions thought to be associated with RA-related sarcopenia, osteopenia, and increased cardiovascular risk. A recently funded extramural study will determine whether treatment of RA with a combination of fish oil and borage seed oil, which are rich in anti-inflammatory unsaturated fatty acid with immunomodulatory properties, is superior to treatment with either oil alone.

Fibromyalgia is a chronic, debilitating disorder that disproportionately affects women. Research demonstrating the therapeutic effectiveness of any single intervention targeting the multi-symptomatic nature of fibromyalgia has remained elusive, and NCCAM-supported investigators have proposed a number of CAM interventions. NCCAM-funded investigators at the Center for Alternative Medicine Research of Arthritis in Baltimore found that mindfulness meditation plus Qigong movement therapy was no better than control (an education support group) in reducing pain or increasing mobility among patients with fibromyalgia. A recently completed pilot study found that fibromyalgia patients receiving individualized homeopathic remedies had decreased tender point pain and improved quality of life and global health when compared with individuals receiving placebo. Additional work is under way to evaluate the effectiveness of intravenous micronutrient therapy, mind/body therapies, and Reiki for the emotional and somatic symptoms of fibromyalgia under double-blind conditions.

Other Bone and Skeletal Diseases

Estimates of 1-year prevalence of back pain indicate that at least 22 percent of the U.S. population reports this problem, with an estimated lifetime prevalence as high as 84 percent. Work-related cases result in over one million lost workdays per year. Direct and

indirect costs for this condition are estimated at $50 billion a year in the United States. In spite of the magnitude of this problem, both the etiology and treatment of back pain remain controversial. Given these facts, it is not surprising that back pain is one of the most common reasons cited for the use of CAM therapies. As noted above, data from the 2002 NHIS survey found that approximately 6.6 percent of adults used CAM for neck pain and 16.8 percent used it for back pains or back problems. Chiropractic and massage are widely used CAM therapies for this condition. NCCAM is supporting studies on the effect of chiropractic, yoga, massage, and acupuncture on both acute and chronic low back pain and chiropractic for neck pain. A recently funded center at the University of North Texas Health Science Center and the Texas College of Osteopathic Medicine will conduct basic and clinical research on the effects of osteopathic manipulation on back and neck strain. One NCCAM-funded study is looking at the effect of acupuncture on low back pain during pregnancy.

Osteoporosis is a well-recognized problem of aging women, resulting in increased disability, chronic pain, and even death among women with spine or hip fractures. Over 50 percent of women who fracture a hip do not regain the level of functioning experienced prior to fracture. Several NCCAM studies on menopausal women (see above) include bone density as an outcome measure in research using botanicals and phytoestrogens. An NCCAM botanical center for age-related disease is conducting a project on isoflavones and osteoporosis. The NCCAM also supports research on the effect of therapeutic touch on markers of bone formation and resorption in women who have suffered a recent fracture of the wrist.

In addition to the program areas outlined above, the NCCAM supports several individual research projects related to other skeletal issues in women. Currently funded as part of the Oregon Center for Complementary and Alternative Medicine Center in Portland is a pilot, phase II trial to evaluate traditional Chinese medicine and Naturopathic Medicine in comparison with usual care for women with temporomandibular disorders.

Breast and Other Cancers

A diagnosis of cancer raises many issues for women, including hope for successful medical intervention to control or cure the disease and the management of toxicity and other side effects of therapeutic intervention. These and other factors may be driving patients' search for alternatives and complements to conventional cancer treatment. A substantial proportion of cancer patients report using CAM therapies in addition to conventional cancer treatment. Studies of terminal cancer patients from different countries found significant use of CAM: 60 percent in Canada reported CAM use; 64 percent in Hong Kong and Taiwan; 61 percent in Austria; 58 percent in Germany; and 42 percent in Norway. In several surveys, similar proportions of male and female cancer patients used CAM, but use was greater among younger patients. A variety of CAM modalities are used by cancer patients, with herbs and herbal teas (Essiac, echinacea, traditional Chinese medicines) being the most frequently reported. Other common CAM modalities include vitamins and minerals (beta carotene, melatonin, enzymes, hydrazine, co-enzyme-Q10); mind-body approaches (imagery/visualization, faith healing, meditation); and biologics (cartilage and mushrooms).

The NCCAM funds the Center for Cancer Complementary Medicine at the Johns Hopkins University, as well as a broad range of research projects on CAM therapies for cancer treatment, including a number of botanicals, acupuncture, healing touch, and mushroom extracts. Some research is clinically focused, such as a study of acupuncture to treat shortness of breath in cancer patients and fish oil supplements for weight maintenance in pancreatic cancer patients.

Other cancer studies are focused on basic research questions, such as the effects of herbs on transcription and cell proliferation and the antioxidant and anti-inflammatory properties of soy and tart cherry. A study of artemisinin, which is derived from the Chinese herb *Aremisia annua*, will look at the ability of this substance, with and without radiation therapy, to kill cervical cancer cells in a mouse model. Another study will examine if and how stearate, which is found in many foods

including chocolate, can inhibit the capability of tumor cells to trigger de-adhesion of breast cancer cells, which would affect metastasis.

Although CAM is used at various stages along the disease continuum, many cancer patients report using CAM therapies 4 to 6 months after the initial diagnosis, a time when ongoing treatment outcomes may be uncertain. Concurrent use of CAM and conventional therapies raise questions about interactive effects. Some NCCAM clinical research projects are looking at the effects of complementary approaches used in the context of conventional treatment while others compare alternative therapies with conventional treatments. For example, one study is looking at the use of ginseng as an adjuvant during standard treatment for breast cancer to understand if it aids or interferes with chemotherapy or hormonal therapy.

Some NCCAM-supported research is looking at the use of CAM to treat side effects associated with chemotherapy. For example, a study at the New England School of Acupuncture will look at the effect of acupuncture treatment on chemotherapy-induced neutropenia in women with ovarian cancer. Other studies are looking at the effects of acupuncture on pain and nausea in women with metastatic ovarian cancer and the use of ginger to control nausea and emesis in patients receiving adriamycin or cisplatin.

The NCCAM also funds several projects that involve women with breast cancer. One study is looking at the effect of massage therapy on lymphedema associated with breast cancer treatment. Another study is focused on interactive effects between soybean phytochemicals and tamoxifen on breast cancer and whether plant estrogens are beneficial or harmful for breast cancer patients.

Healing touch is a biofield therapy that seeks to manipulate hypothesized energy fields around the body. Healing touch is used as a complementary treatment for cancer patients to reduce the side effects of conventional treatments and to maintain immune competency. The NCCAM is supporting an exploratory study to compare the effects of healing touch to conventional care on cellular immune function and short-term side effects of treatment among women receiving chemotherapy and radiation for advanced cervical cancer.

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of mortality for both men and women in the United States. More than 500,000 Americans die of heart attacks each year. Approximately 10 percent of women, ages 45 to 64, have heart disease; this figure is doubled in women aged 65 and older. Common conventional medical treatments for CVD can be invasive and costly; some treatments are less appropriate for cardiovascular disease of women. As the U.S. population turns more frequently to complementary and alternative medicine, it is not surprising that alternative treatments for CVD are popular. The NCCAM supports a diverse portfolio in this area.

The University of Michigan CAM Research Center for Cardiovascular Diseases in Ann Arbor is studying the effectiveness of Reiki to control pain in patients with cardiovascular risk factors and chronic diabetic neuropathy; the use of the botanical, hawthorn, to treat congestive heart failure; and the effect of spirituality and Qi gong on cardiac surgical rehabilitation. The Center for CAM, Minority Aging, and Cardiovascular Disease in Fairfield, Iowa is studying Ayurvedic medicine, a form of traditional Indian medicine that incorporates herbal formulations and meditation, to treat cardiovascular disease in older African Americans. The work at this center includes basic research on the mechanisms of meditation on atherosclerotic cardiovascular disease, a phase II clinical trial of transcendental meditation on carotid atherosclerosis in older Black women, and a study on the mechanisms and clinical effects of traditional herbal antioxidant versus conventional vitamin supplementation on carotid atherosclerosis and other cardiovascular disease risk factors.

The NCCAM is supporting a clinical trial to assess chelation therapy, which is used for a variety of cardiovascular symptoms and diseases. The NCCAM also supports studies looking at the effects of acupuncture and biofeedback on hypertensive patients. Further work is ongoing regarding the effects of a ginkgo biloba extract on vascular function, the effect of grape seed extract on a range of cardiac functions, the cardioprotective effects of American ginseng and yoga,

the consumption of flaxseed meal on lipid metabolism and oxidative stress, and the use of Ayurvedic herbals on lipids and atherosclerosis.

Initiatives

Menopause

The NCCAM has several initiatives related to menopause. As noted above, the NCCAM, along with the NIA, the NIBIB, and the ORWH, issued an RFA for SBIR applications to improve sternal skin conductance technologies to facilitate long-term data collection on hot flash frequency under ambulatory conditions. We expect to make up to five awards in FY 2005. We hope to use this technology in future clinical trials of CAM treatments for hot flashes. In the meantime, we hope to identify other physiologic measures of hot flashes that might be useful to include in clinical studies.

Urinary Tract Infections

Urinary tract infections (UTIs) are a serious and common health problem. Only respiratory infections occur more frequently. Each year UTIs account for more than 9.6 million doctor visits. UTIs are more common in women than men. One woman in five develops a UTI in her lifetime. Among women with a history of UTIs, 20 percent report a second infection, and 30 percent report three or more infections. Most UTIs are caused by a bacteria found in the gastrointestinal tract (*Escherichia coli*). UTIs are generally treated with antibiotics, but these drugs can be expensive, have side effects, and can lead to resistant strains. Cranberry juice is widely used to prevent or treat UTIs. Existing data suggest that cranberry constituents impair adhesion of pathogenic coliforms to uroepithelial cells, a necessary stage in disease pathogenesis, but the data are inadequate to assess the efficacy of cranberry to prevent or treat UTIs, and standardized cranberry products are not available. Thus, in 2002, the NCCAM sought a contractor to develop standardized products for cranberry, a necessary antecedent step for a clinical trial. In 2005, the clinical study will begin enrolling subjects.

The NCCAM has enjoyed and benefitted from its relationship with the ORWH and looks forward to continued collaborative activities.

NATIONAL CENTER FOR RESEARCH RESOURCES

The National Center for Research Resources (NCRR) has a unique responsibility at the National Institutes of Health (NIH): to serve as a "catalyst for discovery." Biomedical research investigators receiving support from the Institutes and Centers (ICs) of the NIH require a broad array of technologies, tools, and materials critical to their research efforts to address health problems. Through its four divisions, the NCRR develops and supports biomedical resources that include: shared sophisticated research instrumentation; specialized animal models for studies of human diseases; flexible support mechanisms to invest in emerging research opportunities; a cost-saving nationwide network of clinical research centers; strong research infrastructure for predominantly minority institutions; infrastructure enhancement and mentorship at institutions in states with little history of NIH funding; and construction, alterations, and renovations to research facilities and animal care centers. Through its support of multidisciplinary research, the NCRR is uniquely positioned to provide funds directly for research, or to act in partnership with other NIH components, in order to address emerging clinical and basic research needs for women's health.

The Division for Biomedical Technology Research and Research Resources supports research on, development of, and access to sophisticated technologies at biomedical technology resource centers. This is accomplished by providing funds for the acquisition of new state-of-the-art shared instrumentation, and by supporting special-emphasis technology development in high performance computing, molecular and cellular structural biology technologies, biomedical engineering, noninvasive imaging and spectroscopy, mathematical modeling, and computer simulations.

The Division for Clinical Research Resources provides clinical research infrastructure for medical scientists who conduct patient-oriented research. This research may be supported by the NIH or by funds provided though other federal, state, and local agencies and the private sector. The division administers programs to increase the opportunities for clinicians to

be involved in patient-oriented research; to procure and distribute a wide variety of human tissues and organs for medical research; to provide vectors for clinical trials of gene therapies; and to support meetings and workshops dedicated to understanding or treating human diseases.

The Division of Comparative Medicine provides high quality, disease-free animal models and specialized animal research facilities for biomedical investigators. Through grants, cooperative agreements, and contracts, this division supports national primate research centers and their field stations, primate breeding and resource-related projects, development of mammalian and nonmammalian animal model resources, postdoctoral training, and a variety of research projects.

The Division of Research Infrastructure expands the nation's ability to conduct biomedical and behavioral research by developing research infrastructure of all kinds. This includes support for construction and renovation of biomedical and clinical research laboratories and animal facilities, recruitment of new faculty, performance of pilot projects, and acquisition of research equipment. Support from this division is provided to predominantly minority-serving institutions that award doctorates in the health or health-related sciences, and to institutions in states that have historically had limited NIH support. This support enables junior college, baccalaureate, and masters degree-granting institutions to significantly enhance their capacity to conduct biomedical and behavioral research by developing and strengthening formal, collaborative agreements with research-intensive, doctoral degree-granting institutions.

The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by NCRR to promote understanding of normal and abnormal physiology in women. In addition, NCRR supports research on prevention and treatment of diseases, disorders, or conditions that are unique to women or have a significant impact on women. Accomplishments include research from centers dedicated to women's health, a mentorship program in women's health, animal models and biological materials, programs that focus on health disparities for minority women, and individual research projects on a variety of health issues related to women.

Accomplishments

The Mayo Clinic College of Medicine, Rochester instituted a multidisciplinary General Clinical Research Center Mentorship Program in Women's Health. The goal of this program is to prepare postdoctoral fellows and junior faculty to become creative, independent clinical researchers in the area of women's health. In the face of declining resources for clinical research, the training program provides intensive exposure to the clinical research environment, a structured mentored program, an understanding of the importance of adherence to regulations regarding clinical research, and substantial training in "survival skills," including effective writing, speaking, grantsmanship, career development, and leadership skills.

The Division of Comparative Medicine (DCM) provides high quality, disease-free animal models and biological materials resources for biomedical investigators through the National Primate Research Centers (NPRCs) and other resources that support women's health research, among many other research topics. DCM-supported women's health research has focused on conditions effecting female reproductive organs, menopause, contraception, reproductive endocrinology, and osteoporosis. Furthermore, the NPRCs provide opportunities for research on reproductive physiology and pathology. Finally, DCM supports women scientists through its veterinary training programs enabling women to advance their professional careers in the veterinary sciences.

The Division of Research Infrastructure (DRI) supported the creation of a new Center of Biomedical Research Excellence (COBRE) for Perinatal Biology at the Women and Infants' Hospital of Rhode Island in FY2003. The center contains research core activities in tissue imaging, laser capture micro-dissection, and real-time PCR for quantification of gene expression at cellular resolution, the breeding of genetically modified mice as models for various aspects of fetal development, and bioinformatics. The theme of this program

is to utilize contemporary approaches in cell and molecular biology to address important issues in the development of the mid-late gestation fetus, and to develop strategies for new therapeutic interventions for fetal and newborn development. Projects include the creation of a transgenic mouse model to study the mechanisms of preeclampsia, which affects 5 to 7 percent of pregnancies and is one of the leading causes of maternal and fetal morbidity and mortality. Creation of a tractable animal model for preeclampsia may enhance understanding and enable the development of effective prophylactic and therapeutic interventions. Other projects address the roles of conserved regulatory proteins and signal transduction pathways in fetal cardiac and lung development. The program currently involves six junior and four senior faculty members from Women and Infants' Hospital and nearby Brown University. There are also plans to recruit new faculty members, and funds for two to four pilot projects annually to enlist existing faculty members to participate in the program. Thus, a total of 20 to 30 investigators may eventually be involved in research related to women's health over the 5-year course of this program.

The DRI also supports a COBRE in Women's Health at the University of Kentucky. The center contains research core activities in imaging, modern genetic and cell biology techniques, the breeding of genetically modified mice as models, and bioinformatics (genomics and proteomics). The theme of this program is the role of female reproductive hormones and selective estrogen receptor modulators in manifestations of health and disease in women. There are five interdisciplinary and interactive scientific projects that include: 1) a study of the mechanisms by which estrogen regulates ovarian function; 2) the effects of estrogen on brain and pituitary function; 3) the role of estrogen in modulating HIV-induced neurodegeneration; 4) the action of estrogen on cognition and mood; and 5) the effects of estrogen on the endothelium and blood pressure. The program involves ten junior faculty members, and 13 mid- or senior-level faculty members from six different departments. Five new faculty members in the area of women's health have been recruited, and two to four pilot projects have been supported annually to enlist existing faculty members to participate in the program. Thus, a total of over 40 investigators will be involved in research related to women's health over the 5-year course of this program.

Ovarian Transplant Results in Newborn Monkeys

Up to 90 percent of women who undergo aggressive cancer therapy while of reproductive age, become sterile because of treatment side effects. One remedy might be to remove and cryopreserve ovarian tissue at the time cancer is diagnosed, and then implant the tissue after the patient is cured of cancer. Toward that end, scientists have demonstrated that ovarian tissue transplants can support the later development of live offspring. This was demonstrated when researchers removed ovaries from seven rhesus monkeys at the NCRR-supported Oregon National Primate Research Center and then transplanted some of each monkey's own ovarian tissue back into the body. Within months, the ovarian tissues resumed secreting hormones and, in some cases, produced eggs. Eggs were removed and fertilized with sperm, and the resulting embryos were implanted into surrogate females. After normal gestations of 5 months, one of these pregnancies resulted in the birth of a healthy infant monkey. The next step will be to attempt this procedure using frozen ovarian tissue, mimicking the same conditions that might eventually be used in women cancer patients.

Topical Microbicide May Be Effective Against Vaginal HIV Infections

Developing effective means for stopping HIV infection in women exposed to the virus is needed. Researchers at the Tulane National Primate Research Center and collaborators from five other institutions have examined a human monoclonal antibody that exhibits neutralizing activity against HIV-1 *in vitro*, by evaluating its ability to inhibit HIV infection in macaques. Following intravaginal application of the monoclonal antibody in female macaques, they were exposed to SHIV. Macaques treated with the antibody were generally protected from infection by SHIV, whereas control animals not treated with the anti-SHIV-specific antibody were not

protected. The antibody could be applied up to 2 hours before SHIV exposure. The results of these studies suggest that the use of neutralizing antibodies inhibits viral entry during sexual transmission and, therefore, may be a potential avenue for reducing HIV infection in humans. Comparison of additional candidate microbicides in the SHIV-macaque model may help identify the most plausible candidates for clinical development.

HDL-associated Estrogen May Be Cardioprotective

Premenopausal women have less cardiovascular disease than men of the same age. The mechanisms for this apparent protection are not known. One possible mechanism involves high-density lipoprotein (HDL), a well-established cardioprotective component of the blood. However, men and women often have similar levels of HDL. Recent studies by several laboratories have demonstrated a previously unknown function of HDL in stimulating the production of nitric oxide. Nitric oxide also has established cardioprotective properties. With funding from the NCRR, researchers at the COBRE in Women's Health at the University of Kentucky have demonstrated that HDL isolated from women contains estrogen. In a landmark *Journal of Clinical Investigation* paper, the authors demonstrated that HDL-associated estrogen stimulates production of nitric oxide by a mechanism that involves the estrogen receptor. Importantly, HDL obtained from postmenopausal women did not contain estrogen and did not stimulate the production of nitric oxide. In contrast, HDL obtained from postmenopausal women undergoing estrogen replacement therapy contained estrogen and stimulated the generation of nitric oxide. These studies establish a new mechanistic paradigm for examining the cardiovascular effects of HDL and estrogen.

The Role of Leptin in Infertility

The relationship between metabolism and reproduction remains a central question in female endocrinology. Leptin, a protein hormone produced from the obesity (ob) gene, acts on the central nervous system to suppress food intake and increase energy consumption. It is also known to play an important role in pubertal development and reproductive capacity, and has been shown to be present at reduced levels in anorexic women. Supported by the NCRR Research Centers in Minority Institutions program, investigators at the Morehouse School of Medicine in Atlanta have utilized a mouse model to elucidate the pathological changes that occur in the absence of leptin. In this model, female mice that lack the ob gene were used. These animals are morbidly obese, infertile, and totally deficient in leptin. The mice exhibited retarded pubertal development as evidenced by delayed vaginal opening and small uteri. Ovarian follicles were reduced in number and also exhibited increased apoptosis (programmed cell death). The lack of leptin thus results in degeneration of the ovarian follicle that, in turn, contributes to infertility.

Genetic Polymorphisms Leading to Increased Risk of Preeclampsia

In an effort to better understand the origins of preeclampsia, one of the leading causes of maternal and perinatal mortality, investigators at the University of Vermont General Clinical Research Center identified a specific maternal genotype variation. The genotype variation is linked to an increased risk of preeclampsia and is associated with reduced plasma volume in young healthy women who have never been pregnant. This finding was consistent with previous literature showing that women with preeclampsia in pregnancy had reduced plasma volume compared to their pregnant peers. The group is continuing its efforts to examine factors that increase or decrease the risk for preeclampsia based on specific genetic predispositions.

Health Effects of the World Trade Center Tragedy on Pregnant Women and Offspring

The impact of toxic air pollutants from the World Trade Center tragedy remains a critical public health concern. Columbia University General Clinical Research Center has taken the lead in conducting an epidemiological study examining the impact of toxic air pollutants from the World Trade Center on the health of pregnant women and infants in lower Manhattan and the surrounding areas.

Lifestyle exposures that might affect birth outcomes, pregnancy complications, spontaneous and induced abortions, and prior birth outcomes will be examined. In addition, participating children will be administered the Bayley-II Scales of Infant Development at 1 and 2 years of age to measure mental growth and psychomotor development.

Initiatives

The NCRR did not issue any specific Request for Applications, Request for Proposals, Program Announcements, or workshops in the area of women's health in fiscal years 2003 or 2004. However, through its support of unique resources, the NCRR contributes a significant portion of its budget to women's health and behavior research. The demand for NCRR-supported resources is determined by scientific and funding shifts. Therefore, future increases in women's health and behavior research supported by other components of the NIH will result in corresponding NCRR increases.

Research on Health Disparities among Special Populations of Women

Parameters of the Menopausal Transition in Hispanic Women in Puerto Rico

The University of Puerto Rico Medical Science Campus, with the support of the Research Centers at Minority Institutions program, has undertaken the first study to develop data on the health status, during midlife and menopause, of Hispanic women in Puerto Rico. Data collected included the distribution of age at menopause, frequency and distribution by age of hysterectomy, and frequency of transition from pre- to perimenopause. In addition, the frequency of diabetes, cardiovascular disease, and osteoporosis were assessed by a self-reported questionnaire. Factors considered were obesity, smoking, exercise patterns, calcium intake, alcohol intake, and medication use. Particular focus was on the influence of lifestyle patterns and stage of menopause upon the annual rate of change in bone density. The researchers assessed body composition and its association with both the experience of menopausal symptoms and osteoporosis. The study also addressed the compliance to the recommendations about osteopenia and osteoporosis given to the participants.

Periodontal Disease, Diabetes, and Preterm Delivery

Preterm delivery is a major healthcare problem affecting one in ten births, and is the leading cause of neonatal death and long-term disability in the United States. Diabetes is a well-established risk factor for preterm delivery. In Hawaii, approximately 20 percent of all women with type 1, type 2, and gestational diabetes deliver preterm. Periodontal disease also contributes to obstetric risk for preterm birth. Researchers at the NCRR-supported Center of Clinical Research Excellence at the University of Hawaii have shown that Asian and Pacific Islander diabetics delivering preterm have significantly more periodontal disease than non-diabetics delivering preterm or at term. This study will obtain data regarding the role of maternal infections (periodontal disease, genitourinary tract infections, and perinatal CMV infection) in preterm birth in diabetic and non-diabetic Asian and Pacific Islander women. Additionally, the newborns will be examined after birth to obtain pilot data regarding the effect of maternal infection on perinatal mortality and neonatal morbidity, as assessed by the presence of chronic lung disease of prematurity and white matter damage in the newborns.

Biometry and Survey Research Core

At Charles R. Drew University of Medicine and Science in Los Angeles, California, the NCRR provides resources to support a Biometry and Survey Research Core to address the need for methodologically sound, culturally and linguistically appropriate strategies in health disparities research. This core has developed a battery of surveys that will be useful in generating data to address disparities in health for African Americans and Hispanics in the areas of diabetes, menopause, and hormone replacement among African American and Hispanic women. This core also supports research focusing on stress reduction and atherosclerotic cardiovascular disease morbidity and mortality in African American women.

Gender Analysis or Sex and Gender Studies during 2003 and 2004

Through its unique role in providing technologies, equipment, building renovations, training opportunities, and infrastructure in its broadest

sense in support of multidisciplinary biomedical research, the NCRR has provided funding for many studies that have analyzed sex and gender differences. Some highlights of this research appear above.

National Center on Minority Health and Health Disparities

The National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads, and coordinates and assesses the NIH effort to reduce and eliminate health disparities. To achieve its mission, the NCMHD employs a multi-faceted strategy to conduct and support research at the basic, clinical, social sciences, and behavioral levels; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. This report provides a summary of the breadth of the NCMHD supported national activities for fiscal years 2003 and 2004, that focus on women's health through its extramural programs and partnerships with the other NIH ICs. The Congress mandated the development of three principal programs within the NCMHD aimed at addressing health disparities—the Loan Repayment Program, the Centers of Excellence Program, and the Research Endowment Program. Additionally, the NCMHD has a Research Infrastructure in Minority Institutions Program (RIMI) and a Minority Health and Health Disparities International Research Training Program (MHIRT) that also support its efforts to tackle the elimination of health disparities.

Accomplishments

NCMHD Loan Repayment Program

The NCMHD has two distinct loan repayment programs: 1) the Health Disparities Research program, which supports the recruitment and retention of highly qualified health professionals to conduct biomedical, clinical, behavioral, community-based, and health services research relevant to health disparities; and 2) the Extramural Clinical Research program, which supports the recruitment and retention of health professionals from disadvantaged backgrounds to conduct clinical research.

Centers of Excellence Program

The NCMHD's Centers of Excellence in Partnership for Community Outreach, Research on Health Disparities, and Training (Project EXPORT) program supports the establishment of Centers of Excellence to conduct research, support research training, and community outreach activities relevant to health disparities. The program seeks to advance the science related to health disparities; create, develop, and evaluate new interventions for preventing, reducing, and eliminating health disparities; and disseminate information useful for improving health via novel partnerships established between Centers of Excellence and health disparity communities.

Research Endowment Program

This NCMHD program builds research and training capacity in institutions that make significant investments in the education and training of individuals from health disparity populations. The program's goals include: the promotion of research; enhancement of the ability of designated health professions schools to support program development, capital improvements, and access to emerging technology; and the recruitment and retention of qualified individuals from health disparity populations that are currently underrepresented in the scientific and health professions workforce.

Research Infrastructure in Minority Institutions Program

The Research Infrastructure in Minority Institutions Program (RIMI) supports institutions that enroll a significant number of students from minority health disparity populations to develop and enhance their capacity and their competitiveness to conduct biomedical research. The RIMI program also assists nondoctoral degree institutions to develop their research infrastructure, primarily through collaborations with research-intensive universities.

Minority Health and Disparities International Research Program

The Minority Health and Disparities International Research Program (MHIRT) was designed to enable U.S. institutions to offer short-term international research training

opportunities for qualified eligible students in basic science, biomedical, clinical, or behavioral research to address global issues related to eliminating health disparities.

The NCMHD also has responsibility for developing and overseeing the implementation of the NIH Health Disparities Strategic Plan, which consists of the 5-year strategy and accompanying budget for combating health disparities for all of the NIH ICs in light of their respective missions. These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities to benefit all affected populations, including women of diverse populations. In addition to the highlights of the NCMHD programs that follow, a noteworthy accomplishment for the NCMHD and the NIH in fiscal year 2004 was the establishment of a new definition for minority health and health disparities and consistent guidelines that the ICs would apply when reporting on minority health and health disparities activities. The new definition for health disparity populations now includes low socioeconomic status and rural populations. This was the result of the work of the NIH Committee on Minority Health and Health Disparities Research Definitions and Application Methodology.

Initiatives

Women's health projects have been supported by the NCMHD in fiscal years 2003 and 2004 through its Centers of Excellence Program, Loan Repayment Program, and through partnerships with the other NIH ICs.

NCMHD Centers of Excellence (Project EXPORT) Program

In 2004, the NCMHD entered its third year of funding under this program. Examples of women's health research and programs that the Centers of Excellence program supported in fiscal years 2003 and 2004 include:

- **Reducing Under-use of Early-stage Breast Cancer Treatment in Minority Communities**
  This project is measuring the extent of under-use of efficacious breast cancer treatments among patients of six hospitals serving East and Central Harlem and other minority communities in lower Manhattan, with the intent of solving problems of under-use of effective interventions in patients with early-stage breast cancer. While still ongoing, this study has generated new knowledge about racial disparities in treatment for early-stage breast cancer; patient and physician reasons for under-use; and is exploring the effectiveness of a simple, sustainable intervention to improve rates of efficacious cancer treatment. To date, they have completed chart abstraction of over 1,000 identified breast cancer cases from six different hospitals. In a study of the records of nearly 700 women, they found an overall disparity in under-use of 19 percent, with the following breakdown: 14 percent under-use for white, 23 percent for Hispanics, and 30 percent for African Americans. They are currently looking for the factors that may explain this under-use data and have completed a small number of patient and surgeon surveys. A computer-based intervention is currently ongoing at three of the six participating hospitals.

- **Increasing Women's Health Literacy on Screening Mammography Using a Multimedia Program**
  In this two-phase project, the goal is to increase the rate of screening mammography of African American women. A computer-based multimedia program educating participants about important breast cancer facts was developed in the first phase of the project and is complete. The second phase, which is ongoing, will involve women in a randomized trial comparing the multimedia program to the use of traditional methods. To date, over 120 participants have been recruited for the second phase of this project.

- **Effectiveness of Culturally Focused Skills Training for Native Children to Enhance Self-concept and Prevent Substance Abuse**
  The goal of this project is to develop and evaluate the effectiveness of social/life skills training with Pascua Yaqui children and assess the impact of their training on their mother's sense of self efficacy regarding resisting alcohol use. To date, 30 children have completed the intervention and, post intervention, the collection of 3 to 5 month follow-up data has been completed. Data analysis has begun and is ongoing.

- **Insulin Resistance and Breast Cancer Among Hispanic Women**
  In this pilot study over 150 women have received diagnostic or screening mammograms, or completed a standardized interview in order to obtain information necessary for assessing the association between insulin resistance and breast cancer risk while accounting for confounding interactions. While Hispanic women are at increased risk for insulin resistance, they have a relatively low incidence of breast cancer. This study may be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

NCMHD Loan Repayment Program

In fiscal years 2003 and 2004, the program funded over 50 researchers conducting research related to women's health including: familial breast cancer, mammography use, and psychological distress among Black women; and influence of behavioral factors on breast cancer survival which addresses the issue of cancer fatigue among individuals undergoing chemotherapy at Howard University Cancer Clinic. An exercise intervention will be developed for cancer patients to aid in addressing the issue of fatigue.

- **Androstenedione Use in Postmenopausal Women**
  This study is to determine the time course and profile of serum androstenedione during a short-term (7 days) treatment with percutaneous androstenedione in healthy, postmenopausal women.

- **Pregnancy, Infection, and Nutrition (PIN): Understanding the Role of Maternal Infections and Adverse Pregnancy Outcomes**
  There is significant racial and ethnic disparity in chronic maternal oral infection, bacterial vaginosis, sexually transmitted diseases, and intrapartum infections. There is also significant disparity in adverse pregnancy outcome. One possible determinant of this relationship is that women of different ethnic groups have different rates of placental growth and development, perhaps due to differential expression of placental growth factors. There has been little data to explore differential expression of placental growth factors in racial/ethnic minorities, or in women with antepartum infection. The Pregnancy, Infection, and Nutrition (PIN) study, a large, prospective cohort study of pregnant women, is designed to examine the relationship of placental vascular pathology to preterm birth. The project will analyze the relationship between markers of placental proliferation and cell death and adverse pregnancy outcomes (preterm birth < 37 and < 34 weeks, delivery of a growth-restricted infant, preeclampsia). The role of maternal factors, such as smoking or infection, in the causal pathway of adverse pregnancy outcome will be evaluated with a focus on the extent to which these factors affect placental cell proliferation and cell death. Racial/ethnic disparity in placental pathology, placental cellular proliferation, and placental cell death will be examined.

- **Family PACT (Planning, Access, Care and Treatment) Program Support and Evaluation – California's Reproductive Health Program for Low-income Residents; and Barriers to Family Planning Among Mexican Immigrants in California: Gender, Power, Culture**
  This research project will build upon the sociological understanding of gender and the social structure of inequality by investigating the reproductive health of disadvantaged populations and their access to reproductive health services. It will examine the role of gender and other sociocultural factors in influencing contraceptive behavior, and will seek to broaden demographers' and health researchers' understanding of the need for family planning services. The project will examine both men and women's reproductive health. This is particularly important because men underutilize and undervalue reproductive health services, yet men's reproductive health has received relatively little attention. This affects men, but it also affects women through men's failure to use or cooperate in contraception—resulting in unintended pregnancies—and the transmission of sexually transmitted infections.

- **Characterization of the Granulin–Epithelin Precursor in Endometrial Cancer Between African Americans and Caucasians**
  African American (AA) women with endometrial cancer have a worse clinical outcome, stage-for-stage, corrected for incidence, than their Caucasian American (CA) counterparts. Epidemiologic studies have failed to identify access to care as a cause for this racial disparity, suggesting underlying molecular mechanisms for these differences. African American women have been shown to have a higher incidence of estrogen receptor (ER)-negative tumors and are poor responders to hormone therapy. A molecular basis for the difference in clinical outcome between patients with ER-positive endometrial tumors and those with ER-negative tumors has not been determined. The hypothesis is that a novel estrogen regulated growth factor, the granulin-epithelin precursor (GEP), may mediate endometrial cancer cell growth. The investigators discovered a high frequency of GEP expression in invasive epithelial ovarian cancer (OVCA) epithelium, when compared to low malignant potential (LMP) ovarian tumor epithelium, by cDNA library analysis. LMP tumors differ from invasive OVCA by the inability to invade their underlying stroma. In addition, patients with LMP tumors have a 10 to 20 year survival advantage over those with invasive OVCA. It was further confirmed that GEP is a growth factor for OVCA cells using anti-sense GEP transfection experiments. GEP expression has also been shown to be high in ER-negative breast cancer cells and is upregulated by estrogen in ER-positive breast cancer, suggesting a role for GEP in female cancers. The specific aims of this study are to investigate GEP production, secretion, and its estrogen regulation *in vitro* and *in vivo*. GEP will be characterized in two endometrial cancer cell lines: the well-differentiated, ER-positive, HEC-1A cells; and the poorly differentiated, ER-negative cell line, KLE cells. GEP expression will also be assessed by immunohistochemistry in a pilot cohort of 50 age- and stage-matched AA and CA women with defined ER/progesterone receptor (PR), PTEN, and p53 mutation status and known clinical outcome. GEP expression will be evaluated against ER/PR status, race, histology, PTEN, and p53 mutation status. Defining a new growth factor for endometrial cancers may broaden the understanding of the biology of this disease and may be a new molecular target for at-risk women. In addition to characterizing GEP as a steroid-regulated growth factor for endometrial cancer, the study will be extended to evaluate the contribution of genetic polymorphisms to poor clinical outcome in endometrial cancer.

- **Quality of Breast Cancer Care: The Role of Hispanic Ethnicity, Language, and Socioeconomic Position and the Impact of Structure on the Quality of Breast Cancer Care**
  The large gap in our understanding of the causal mechanisms underlying health disparities points to the need for research based on a conceptual framework that integrates medical, social, and cultural dimensions of care including the structure of the health services delivery system, patient characteristics including SEP (such as income, poverty, wealth, and education, at both the individual and community level), cultural and linguistic background, and baseline health status, and how these factors influence the processes and outcomes of care. The specific aims of this project are: 1) to enrich an existing, clinically extensive survey data set collected from a diverse population-based sample of women in Los Angeles County with breast cancer with data from the census; 2) geo-code patient and provider data, mapping them to the census tract level; 3) derive indicators at the census-tract level of SEP and distance to providers of cancer care; and 4) examine the relative importance of ethnicity, language, SEP, and how they relate to the structural characteristics of settings in which women receive care, the care women do and do not receive and, ultimately, to patient outcomes, particularly for the population-based sample of Hispanic and non-Hispanic white women with breast cancer.

- **HIV/Alcohol and Other Drug Use Prevention in Female Adolescent Detainees**
  The proposed investigation aims to apply and test a model for delivering a HIV risk reduction and alcohol and drug-related intervention to female adolescent detainees (FADs). This model is designed to reduce alcohol and other drug use (AOD), risky sexual behavior (RSB), AOD-related HIV risk behavior (AOD/HIV), and delinquency through a comprehensive intervention that integrates principles for behavioral change set forth by social cognitive and problem behavior theories. An intervention will be evaluated with a randomized longitudinal design that will compare FADs entering two Georgia Department of Juvenile Justice (DJJ) facilities across two conditions. Participants in one condition will receive a facility and community-based AOD/HIV risk reduction intervention (INT). Participants in a second condition will receive the standard education provided in the facility (CTRL). The specific aims for this study are: 1) to test the components of a problem behavior and social cognitive theory (SCT)-based HIV/AOD risk reduction intervention for FADs designed to reduce alcohol and other drug use (AOD), risky sexual behavior (RSB), AOD-related HIV risk behavior (HIV/AOD), and delinquency, as well as positively modify knowledge, attitudes, and beliefs believed to mediate these outcomes; 2) to determine whether the mediators (e.g., AOD/HIV knowledge, self-efficacy to avoid HIV risk behavior, and AOD expectancies for social and sexual enhancement, self-efficacy for sexual communication/negotiation, sex-role stereotyping, family, and community involvement) explain or statistically account for differences in intervention outcomes over time; 3) to assess whether the effects of the intervention components are moderated by processes associated with service delivery (e.g., number of sessions received); and 4) to test a programmatic strategy for participant retention.

- **Obesity among African American and Latino Youth: Assessing Behaviors in the Context of Family and Community Environments**
  This research includes two projects that explore factors associated with the development of obesity in African American and Latino youth. Project 1 explores the influence of culture and social traditions on factors that are related to obesity, such as perception of parental influence on physical activity and body esteem of African American and Latina preadolescent girls. Project 2 examines similarities and differences in coping responses (e.g., weight-related eating behaviors) to perceived environmental challenges in African American and Latino youth. Project 3 plans to gain more experience in the design and implementation of intervention and prevention programs that address obesity among youth by partnering with communities and schools. This will be accomplished through involvement in the Girls Health Enrichment Multi-site Study (GEMS) and adding an additional component.

- **Neighborhood Risk Factors for Maternal Depression**
  The proposed research projects will lead to future longitudinal studies on the effects of the social and physical environments on maternal depression and changes in depressive states and symptomatology over time. Study 1 is a study of a sample of women in Washington, DC designed to elucidate how and why neighborhoods impact residents. Study 2 is a cross-sectional study of mothers in mid-to-low SES neighborhoods with and without depressive symptoms, assessed by a symptom checklist. The goal of this study is to identify how structural neighborhood characteristics contribute to the presence of depressive symptoms. This study addresses the distribution of depressive symptoms by degrees of low neighborhood SES for African American mothers.

- **Racial and Ethnic Disparities in Physical and Mental Health**
  The research activities will consist of utilizing the Americans' Changing Lives (ACL) dataset to explore racial/ethnic disparities in physical and mental health on a population level. The project's original aims were to: 1) understand and document the ways in which a range of activities and social relations that people engage in during middle and later life are "productive," that is, contribute toward maintaining or enhancing

the health and effective functioning of themselves, other people, or the larger society; 2) understand the social, psychological, and economic factors that promote or inhibit health, effective functioning, and productive activity during the middle and later years of life; 3) investigate sociocultural variation in the nature, meaning, determinants, and consequences of productive activity and relationships, focusing especially on differences and similarities in these regards between Black and white Americans. During the next phase, the project will utilize existing data from a nationally representative four-wave panel study (collected in 1986, 1989, 1994, and 2001/2002) to understand socioeconomic and racial health disparities. This phase will seek: 1) to continue and enhance ongoing analysis by extending prospective followup to 16 years, allowing for better analysis of: a) time-varying covariates, b) the impact of changes in risk factors on changes in health, and c) potential reciprocal relationships between and among SES, psychosocial risk factors, and health; 2) to enhance and improve the measurement of a number of variables already being considered in ongoing analysis, including SES (e.g., improving assessment of wealth), productive activities, religious beliefs and behaviors, and personality or dispositional factors (e.g., hostility, optimism, hopelessness, and John Henryism [i.e., the strong behavioral predisposition to directly confront barriers to upward social mobility]); 3) to add new measure to ACL 4 (2002; via archival data) to all waves of data for both medical care and exposures in physical and social environments; and 4) to undertake more focused analyses of racial/ethnic differences in health and explanations of them.

Collaborations

The NCMHD works with other NIH ICs to leverage its resources in an effort to expand its capacity to eliminate health disparities from a broad spectrum of disciplines.

- **The Sister Study**
  A project of the National Institute of Environmental Health Sciences (NIEHS), with co-funding from the NCMHD, this is the only long-term study of women, aged 35 to 74, whose sister had breast cancer. It is a national study to learn about environmental and genetic causes of breast cancer. In the next 3 years, 50,000 women who live in the United States and who have had at least one sister with breast cancer and do not have breast cancer themselves will be asked to join the study. The Sister Study will collect information about exposures before a woman's body has been changed by breast cancer, its treatment, or changes she might make in her lifestyle after being told she has breast cancer. Researchers will be able to compare this information between women who do and do not get breast cancer. Because the exposures and lifestyle factors will have occurred before the diagnosis of breast cancer, that information will help to reveal more about what leads to breast cancer. Women in the study will provide information about a wide range of exposures and lifestyle factors throughout their lives and give us a blood sample, toenail clippings, and a dust sample. Women will be weighed and measured and will fill out several questionnaires. We will contact women in the study each year to find out current health information. This wealth of information will answer many questions about breast cancer risks, including the combined effects of genes and environment.

- **Alcohol, Violence, and Health Services in Rural Women**
  A collaborative project with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) with the following specific aims: 1) to describe similarities and differences in health service use patterns and victimization experiences among intimate violence victims with protective orders stratified by alcohol use—those who drink alcohol heavily (n = 250), those who drink alcohol (n = 250), and those who do not use alcohol (n = 250) in rural and urban areas; 2) to examine the effect of alcohol use on the nature, extent, and co-occurrence of health service utilization and victimization patterns among rural and urban women who have a protective order; 3) to examine the association of social support, positive

health practices, access to health care, perceptions of health care needs and beliefs, and stress with alcohol use and health service utilization among rural and urban women who have a protective order; and 4) to examine changes in alcohol use, intimate violence victimization, and health service utilization over a 1-year period from baseline to followup among rural and urban women who have protective orders.

- **Patient-oriented Research: Systematic Lupus Erythematosus**
  The research goals of this co-funded award with the National Institute of Arthritis and Musculoskeletal and Skin Diseases are: 1) to continue ongoing lupus research activities (osteoporosis, genetics, and cancer); 2) to pursue new research opportunities (cardiovascular disease); 3) to participate as a preceptor for a trainees' thesis project for the Masters of Public Health Program; and 4) to mentor medical students, residents, fellows, and junior faculty in their area of clinical research.

- ***Trichomonas Vaginalis* Genetic Analysis of Cell Adherence**
  The NCMHD co-funds this research study in conjunction with the National Institute of Allergy and Infectious Diseases. Trichomonas vaginalis is responsible for serious health consequences for women. Significantly, the infection by this parasite is a co-factor in amplifying the transmission of HIV among African American and Hispanic women contributing to poor minority health and health disparities in our nation. The long-term goal of this study is to understand the molecular basis of pathogenesis. The structure, function, and regulation of *T. vaginalis* AP65 adhesin compartmentalization will be examined in this study. The hypotheses being tested are: i) iron regulates gene expression, compartmentalization, and surface placement of all members of the ap65 gene family; ii) there is cross signaling by phosphorylation of trichomonads and AP65 following adherence; and iii) there is a quantitative relationship between host epithelial cell receptors for AP65 and levels of cytoadherence.

- **Epidemiology of Systematic Lupus and Cardiovascular Disease**
  The National Institute of Arthritis and Musculoskeletal and Skin Diseases funds this project with co-funding from the NCMHD. Systemic lupus erythematosus (SLE) is the prototypic systemic inflammatory autoimmune disease that affects predominantly young pre-menopausal women. African American women are afflicted three to four times more frequently than Caucasian women. The risk of myocardial infarction in women with SLE is up to 50 times higher than expected in women aged 35 to 44 years, a population of women that should otherwise be protected from such risks. This study will: 1) compare the prevalence and extent of subclinical vascular disease in 200 SLE patients and matched controls. Subclinical disease will be defined by calcification of the coronary arteries and aorta as measured by electron beam CT, and carotid plaque and intima media thickness as measured by B mode ultrasound. Patients will be recruited from the Pittsburgh Lupus Registry; 2) determine whether the risk factors associated with subclinical vascular disease in patients with SLE are different from controls. Traditional, inflammatory, and immunological factors will be measured; and 3) determine the risk factors associated with progression of carotid atherosclerosis over a 3-year period in women with SLE. It is important to determine the burden of atherosclerosis in this unique population, examine potential risk factors, and ultimately design intervention and prevention trials.

- **A Novel HOX Gene Target in Breast Cancer**
  The NCMHD co-funds this National Cancer Institute's study, which will test the hypothesis that BP1 is a new therapeutic target in breast cancer by analyzing additional tumors and using molecular techniques. Currently, BP1 in breast tumors by RT-PCR are being measured. In this application, immunohistochemical analysis will be developed to facilitate analysis of BP1 expression in histological sections. Of relevance to this grant, previous molecular studies in leukemia suggest that BP1 expression is transforming and is required for survival of a leukemia

cell line. If BP1 is part of an anti-apoptotic pathway, its expression may be important in breast cancer cells as well. Stable breast cancer cell lines overexpressing BP1 will be established to determine whether BP1 expression is transforming *in vitro*. Analysis of a gene array using these cell lines will help to identify genes that may be targets of BP1 and pathways in which it is involved. To determine whether decreasing BP1 levels leads to growth inhibition or apoptosis, BP1 expression will be reduced in breast cancer cell lines using genetic and pharmacological methods. This study will, therefore, combine clinical and genetic approaches to determine the importance of BP1 expression in breast cancer.

- **Adherence in Recently Sober HIV Women: Ecosystem TX**
  This National Institute of Drug Abuse application, which is supported by the NCMHD, proposes a structural ecosystemic intervention for HIV medical adherence (SETA) in recently sober women. Recently sober is defined in this proposal as DSM IV drug dependence or abuse within the last year, but not in the last 60 days. The 4-month intervention targets women, their families, and their social networks as the building blocks for the infrastructure to support HIV medical adherence, reduction in HIV transmission risk behaviors, and drug abuse relapse prevention. An important part of this infrastructure is a constructive relationship between the HIV-infected women and their health care system. The study will enroll 196 women and randomly assign them to either the SETA intervention, or an HIV health group designed to match SETA for attention. Women are assessed at 2-month intervals for a period of 12 months. HIV medical adherence is measured by self-report, MEMS CAP, and viral load. The SETA intervention is hypothesized to improve HIV medical adherence relative to the HIV health control group.

- **Periodontal Disease in Diabetic Women with Preterm Birth**
  This National Institute of Dental and Craniofacial Research project, co-funded by the NCMHD, seeks to establish a collaborative study partnering the periodontal and molecular epidemiology expertise at the University of North Carolina School of Dentistry with the Obstetrics/Gynecology expertise at the University of Hawaii School of Medicine to examine the role of periodontal disease in preterm deliveries among pregnant diabetic Asian and Pacific Islander (API) women. The specific aim of this proposal is to conduct a pilot case-control study to determine the extent of periodontal disease in API diabetic (type 1, type 2, or gestational) and nondiabetic women who have term and preterm deliveries (< 37 weeks gestational age).

NATIONAL EYE INSTITUTE

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States.

Several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion that in most cases causes mild discomfort, but in more severe cases may result in corneal scarring and blindness; corneal endothelial dystrophy, a slowly progressive disease that occurs when endothelial cells deteriorate as a result of cell loss, age, or trauma-induced keratoconus, a visually disabling thinning disorder of the central cornea that results in irregular astigmatism, progressive corneal distortion, and corneal scarring; and age-related macular degeneration, a deterioration of the region of the retina that is responsible for high-resolution vision.

Accomplishments

Optic Neuritis

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year, primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. Results from the ONTT showed that oral corticosteroid, the most common treatment of the disease, when used alone is ineffective in treating the disease and actually increases a person's risk for future attacks; whereas intravenously administered corticosteroids promoted more rapid recovery and did not increase the rate of recurrence. Based on data collected from 2 years of followup of patients enrolled in the ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis. The results from this research offered the first scientific evidence that intravenous corticosteroids help to delay the progression of multiple sclerosis. This study also demonstrated that the presence of multiple enhancing brain lesions found on magnetic resonance imaging (MRI) scan performed at the time optic neuritis was diagnosed was the single most important predictor of the development of multiple sclerosis within 5 years. The Longitudinal Optic Neuritis Study (LONS), which will follow patients originally enrolled in the ONTT, is underway.

Dry Eye

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands, or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, such as Sjögren's syndrome, an autoimmune disorder, but also occurs in association with aging, nerve dysfunction, radiation therapy, and with antidepressant and anti-psychotic drug therapy.

Lacrimal insufficiencies affect roughly two million Americans, particularly postmenopausal women. NEI-supported researchers are investigating the hypothesis that lacrimal insufficiency is triggered by loss of hormonal support for the lacrimal gland's secretory capacity. Much of the dry eye disease that afflicts women after menopause, during oral contraceptive use, pregnancy, lactation, and the late luteal phase of the menstrual cycle appears to be attributable to lacrimal gland atrophy following decreases in available androgen levels. In addition, new findings suggest that the pathogenesis of dry eye may have an autoimmune component; thus, tying it to Sjögren's syndrome.

Corneal Endothelial Dystrophy

Corneal endothelial dystrophy is a slowly progressing disease of the endothelium that usually affects both eyes and is more common in women than men. Although physicians can often see early signs of the disease in people in their 30s or 40s, the disease rarely affects vision until a person reaches their 50s and 60s.

The corneal endothelium is a layer of cells, which line the inner surface of the cornea. The endothelial cells are responsible for pumping fluid out of the cornea. The cornea is normally clear despite being bathed in tear on the outer surface and in aqueous humor on the inner surface. This clarity is maintained by the endothelial cell layer. If endothelial cells are diseased or absent, permanent corneal edema, loss of corneal transparency, and eventual blindness may occur.

NEI-supported scientists are attempting to determine why endothelial function deteriorates following cell loss, age, or trauma. Delineating the optimal conditions for the tissue culture of corneal endothelium will help evaluate the problems involved in transplanting these cultured cells and assuring their survival. With further refinement of endothelial culture techniques, it will be possible to determine whether cell-cycle stimulatory and inhibitory factors arise from other cells and whether the endothelium can be induced to

repair itself. Parallel gene therapy studies are being pursued in animals with the aim of developing vectors to deliver factors therapeutically to the eyes of patients with the disease.

Keratoconus

Keratoconus occurs when the middle of the cornea thins and gradually bulges outward, forming a rounded cone shape. This abnormal curvature changes the cornea's refractive power, producing moderate to severe distortion (astigmatism) and blurriness (near- and farsightedness) of vision. These changes may also disrupt the normal, light-conducting arrangement of corneal protein, causing swelling and a sight-impairing scarring of the tissue. Keratoconus has become better understood through investigations into the genetic predisposition of the disease, detection of early forms of the disorder using computerized topographic analysis, and advances in understanding the enzymology that underlies corneal thinning. Microarray technology is highly valuable in developing profiles of diseased tissue and comparing them to those of normal tissue.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is a NEI-supported multicenter, observational study designed to characterize the progression of keratoconus over a broad spectrum of disease severity. Information on participants' vision, quality of life, corneal shape, and corneal scarring is being collected to characterize the disease pathology and to identify risk factors and protective factors that determine the severity and progression of the disease. Investigators are continuing to conduct patient follow-up examinations.

Age-related Macular Degeneration

Age-related macular degeneration (AMD) is not only the leading cause of blindness in patients over the age of 65, but is now the most common cause of blindness in the United States. The incidence of AMD continues to rise in the population. Women have 50 percent greater risk than men for AMD.

The macula is a specialized region near the center of the retina responsible for high-resolution vision that permits activities, such as reading. Degeneration of this region is believed to be the result of a complex set of interactions involving genes/gene products and environmental factors. A high priority has been placed on identifying predisposing genes, their products, and what environmental factors impact these gene products to produce or protect against the disease. The Age-related Eye Disease Study is a multicenter clinical trial/epidemiological study, now in its 11th year, designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. A second multicenter clinical trial, the Complications of Age-related Macular Degeneration Prevention Trial, will assess the safety and efficacy of laser treatment in preventing vision loss in patients with bilateral disease. The Incidence of Late Macular Degeneration in Older Women study aims to determine the incidence, progression, and association with other co-morbid factors, such as diabetes and cataract surgery, on age-related macular degeneration in women over 80.

Initiatives

The NEI and the National Advisory Eye Council (NAEC) have established in its strategic plan, A National Plan for Eye and Vision Research, goals, objectives, and research priorities for improving visual health and preventing blindness, including diseases that have a higher incidence and prevalence for women than for men. These include studies on:

- **Optic Neuritis**
  Research priorities are to develop an animal model of this disease to better understand the pathogenesis of the disorder, to develop immunomodulating therapies to limit optic nerve damage from inflammation, and to understand the relationship between optic neuritis and multiple sclerosis.

- **Dry Eye**
  The overall objective is to determine the role of sex hormones on lacrimal gland function. A body of experimental evidence supports the notion that androgen sex hormones and prolactin modulate lacrimal gland function, thus providing an explanation for the observed gender bias of this condition and suggesting hormone modulation as a possible treatment.

- **Corneal Endothelial Dystrophy**
  Research priorities are aimed at understanding the biologic and functional structures of endothelial cells.

- **Keratoconus**
  An overarching objective is to understand the genetic basis of keratoconus. Identification of gene loci and their encoded proteins should provide clues to the pathogenesis of the disease and suggest new therapies.

- **Age-related Macular Degeneration**
  Research priorities are aimed at identifying the cellular, molecular, and systemic factors that are involved in the pathophysiology of AMD. Because of the complexity of this disease, studies that use a combination of epidemiology, basic cellular and molecular biology approaches, and genetics are being pursued.

- **Glaucoma**
  Retinal nerve fiber layer thickness appears to be influenced by estrogen levels. A longitudinal study is being conducted to determine the effects of female hormones on these measures of glaucomatous damage.

- **Cataracts**
  A role for estrogen in the pathophysiology of cataract formation has been observed. However, the evidence is unclear whether this role is protective or deleterious. Studies are underway to determine how estrogen influences the development of cataracts.

The Women's Health Initiative Observational Study affords the NEI the opportunity to pursue epidemiological studies in women-only cohorts. This will allow gender-specific analyses of risk factors in major blinding and debilitating diseases. The following study is ongoing:

- **Carotenoids and Age-related Eye Disease in the Women's Health Initiative**
  This initiative will follow a cohort of women enrolled in three of the Women's Health Initiative Observational Study sites to assess the role of dietary xanthophyll carotinoids in preventing the development of age-related macular degeneration and cataract.

The NEI is working with the National Institute of Dental and Craniofacial Research (NIDCR) and the Office of Research on Women's Health (ORWH) to enhance research opportunities in the diagnosis, epidemiology, and treatment of Sjögren's syndrome.

- **NIDCR International Workshop on Sjögren's Syndrome**
  Along with the ORWH and the Sjögren's Syndrome Foundation, the NEI co-sponsored this workshop, April 10-11, 2003. The purpose was to develop outcome measures for clinical research in Sjögren's syndrome.

- **International Sjögren's Syndrome Registry**
  The NEI is co-funding a NIDCR initiative for the development of an International Sjögren's Syndrome Registry. The ultimate goal of the registry is to promote cutting-edge research in the area of Sjögren's syndrome with emphasis on diagnosis, epidemiology, causes, prevention, and treatment. The coordinating center is at the University of California–San Francisco; four clinics in Argentina, China, Denmark, and Japan will participate in the registry. A "Baseline Eye Exam Form" and a "Baseline Eye Exam Standard Operating Procedures" were among the accomplishments of the group during in the first year of funding.

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. It plans and conducts—through work in its own laboratories and through grant- and contract-supported activities in extramural scientific institutions—an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of the diseases under its purview and to the clinical use of blood and all aspects of the management of blood resources. For more than 30 years, the NHLBI Office of Prevention, Education, and Control has supported educational programs for physicians, patients, and the general public to improve awareness,

diagnosis, treatment, and prevention of diseases and conditions under the institute's purview. Since FY 1993, the institute has been the home of the National Center on Sleep Disorders Research and, since FY 1998, it has had responsibility for the NIH Women's Health Initiative (WHI).

Highlights of NHLBI-supported activities during fiscal years 2003 and 2004 include the following:

- **WHI Postmenopausal Hormone Component**
  The WHI reported the main outcome of its trial of estrogen in women with a hysterectomy. Other publications provided detailed information about the effects of estrogen plus progestin on health-related quality of life, stroke, gynecologic cancers, bone health, and colorectal cancer.
- **Women's Ischemia Syndrome Evaluation (WISE) Study**
  This study, which has been examining issues of relevance to diagnosis of chest pain and myocardial ischemia in women, produced a number of new findings regarding predictors and correlates of cardiovascular disease risk.
- **Women's Heart Health Education Campaign, The Heart Truth**
  This campaign greatly expanded its activities to raise public awareness that heart disease is the leading cause of death among women in the United States, and that many things can be done to prevent it.

Accomplishments

Women's Health Initiative

The WHI is a 15-year study of strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in postmenopausal women. Launched by the NIH in 1991, it has been administered by the NHLBI since fiscal year 1998. More than 160,000 women from across the United States, who were between 50 and 79 years of age at the time of their recruitment, are enrolled in the WHI clinical trials and observational study; almost 30,000 of the participants are minorities. The clinical trial component consists of three prevention studies examining the effects of postmenopausal hormone therapy on risk of coronary heart disease (CHD), osteoporosis, and breast cancer; the effects of a low-fat diet on risk of breast and colorectal cancers and CHD; and the role of calcium and vitamin D supplementation in preventing fractures and colorectal cancer. The observational study component has focused on identifying predictors of disease. In addition, a Community Prevention Study was conducted in collaboration with the Centers for Disease Control and Prevention to examine strategies for enhancing adoption of healthful behaviors, particularly among minority and underserved women.

The WHI postmenopausal hormone trial included two placebo-controlled components—a study of estrogen plus progestin in women who had an intact uterus and a study of estrogen alone in women who had undergone a hysterectomy. Both studies were designed to test the hypothesis that long-term use of hormone therapy could reduce risk of CHD. As reported previously, the estrogen-plus-progestin trial was halted ahead of schedule in July 2002. Compared with women taking a placebo, study participants taking hormones experienced higher rates of heart attack, stroke, blood clots, and invasive breast cancer. Although the women taking hormones also had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable.

Trial of Estrogen in Women with Hysterectomy

In March 2004, the second WHI postmenopausal hormone trial component also was halted ahead of schedule. With an average of nearly 7 years of followup completed, the trial revealed that estrogen-alone therapy had no effect on CHD risk, but it increased risk of stroke. No evidence of elevated breast cancer risk was found, and a favorable effect on bone health emerged. On balance, however, the trial indicated that postmenopausal hormone therapy should not be prescribed for chronic disease prevention, but only for short-term relief of menopausal symptoms. The results from the WHI hormone therapy trials have provided women and their physicians with a scientific basis for making informed decisions about hormone therapy use. (*Journal of the American Medical Association*, April 14, 2004)

Estrogen Plus Progestin and Health-related Quality of Life

The WHI collected information on a variety of health-related quality-of-life measures at the beginning of the trial and 1 and 3 years afterward. They found that women assigned to take estrogen plus progestin did not experience any significant changes in general health, physical or emotion limitations on usual role-related activities, vitality, social functioning, mental health, depressive symptoms, or sexual satisfaction. Moreover, hormone treatment was associated with only very modest and transient improvements in sleep disturbance, physical functioning, and bodily pain. These small benefits do not appear to outweigh the risks of heart attack, stroke, blood clots, and breast cancer that are associated with estrogen-plus-progestin therapy. (*New England Journal of Medicine*, May 8, 2003)

Estrogen Plus Progestin and Stroke

As noted above, the estrogen-plus-progestin trial was stopped early because treatment was associated with adverse effects, including stroke. Overall, 151 women assigned to take estrogen plus progestin and 107 women assigned to take a placebo had strokes, most of which were ischemic. Further analysis was conducted to determine whether it was possible to identify characteristics of the women taking hormones that rendered them particularly susceptible to stroke. Results indicated that the excess risk of stroke affected women regardless of age, hypertension, prior CVD, or prior use of hormones, statins, or aspirin. Moreover, accounting for other stroke risk factors, including smoking, diabetes, and blood levels of various indicators, did not alter the effect of the hormone regimen on stroke risk. The researchers concluded that estrogen plus progestin increases the risk of ischemic stroke across the board in healthy postmenopausal women. (*Journal of the American Medical Association*, May 28, 2003)

Estrogen Plus Progestin and Gynecologic Cancers

During 5.6 years of followup in the WHI estrogen-plus-progestin trial, invasive gynecologic cancers were diagnosed in 111 women. A 58-percent increase in ovarian cancer and a 19-percent decrease in endometrial cancer were observed in women assigned to hormones, relative to those given placebos, but these findings were not statistically significant (i.e., they may represent a chance occurrence). However, women in the hormone group required significantly more endometrial biopsies (33 versus 6 percent), and twice as many of them required multiple biopsies as did women in the placebo group. The increased need for diagnostic procedures in response to bleeding represents an additional factor that must be considered in a woman's decision to use postmenopausal hormone therapy. (*Journal of the American Medical Association*, October 1, 2003)

Estrogen Plus Progestin and Bone Health

At the time the estrogen-plus-progestin trial was halted because of adverse effects, a significantly decreased risk of fractures was apparent among its participants who were assigned to take hormones. A subsequent analysis sought to determine whether the extent of benefit varied according to a woman's susceptibility to sustain fractures, as determined by levels of known risk factors. Investigators found that the effect of the combined hormones on risk of fracture did not differ according to age, body mass index, smoking status, history of falls, personal and family history of fracture, total calcium intake, past use of hormone therapy, or bone mineral density. When the women were categorized as having low, medium, or high fracture risk according to a summary score, no evidence was found that the efficacy of estrogen plus progestin differed among the three groups. When these results were considered in light of the overall trial findings with respect to important disease outcomes, it was apparent that hormone therapy conferred no net benefit, even among women deemed to be at high risk of fracture. (*Journal of the American Medical Association*, October 1, 2003)

Estrogen Plus Progestin and Colorectal Cancer

WHI participants who were assigned to take combined hormone therapy developed colorectal cancer during the subsequent 5.2 years at about half the rate of those given a placebo. Further analysis considered additional follow-up data and assessed the features of the colorectal cancers that occurred in the hormone group versus the placebo group.

The invasive colorectal cancers in the two groups were similar in location, tumor grade, and histologic features. However, the women assigned to hormone therapy who developed cancer had greater lymph-node involvement and their cancer was diagnosed at a more advanced stage. Although the reasons for these phenomena are unknown, the findings suggest the importance of bowel screening among postmenopausal women who use hormone therapy. (*New England Journal of Medicine*, March 4, 2004)

WHI: Selected Results from the Observational Study

The WHI Observational Study (OS) includes over 93,000 postmenopausal women, between the ages of 50 and 79, who are being followed for an average of 9 years. Its goals are to provide reliable estimates of the extent to which known risk factors predict heart disease, cancers, and fractures; identify new risk factors for these and other conditions in women; correlate risk factors and presence of disease at the start of the study with subsequent disease incidence; and create a resource for identifying biological indicators of disease, especially in the blood.

Statin Use and Bone Health

Osteoporosis affects millions of older women, placing them at increased risk of bone fractures. Some, but not all, recent observational studies have raised the possibility that treatment with statins—drugs that are usually prescribed to lower blood cholesterol levels and thereby prevent CHD—may also prevent bone fractures. WHI–OS investigators examined this issue in their large cohort of postmenopausal women, which included nearly 8,000 statin users. They found that women who were taking statins at the start of the study, regardless of how long they had been doing so, experienced rates of bone fractures similar to those of women who did not take statins. Moreover, bone density levels were not significantly different between users and non-users of statins. Investigators concluded that current evidence does not support prescribing statins to prevent or treat osteoporosis in postmenopausal women. (*Annals of Internal Medicine*, July 15, 2003)

Physical Activity and Risk of Breast Cancer

A number of studies have found that women who are physically active are less likely to develop breast cancer than women who are sedentary. However, the type of activity that may confer such a benefit and its optimal duration and timing have been unclear. Using the detailed assessments of physical activity reported by women who entered the WHI–OS, investigators analyzed associations between incidence of breast cancer and exercise, both past and present. Results showed that women who had engaged in regular strenuous physical activity when they were younger were not as likely as their less-active counterparts to develop breast cancer later in life. Moreover, physical activity lowered breast cancer risk among women who began to exercise later in life or who exercised only moderately (e.g., walked briskly for 1.25 to 2.5 hours per week). Although the results suggest longer duration of exercise is better in terms of reducing breast cancer risk, they also indicate that the activity need not be strenuous to yield some benefit. (*Journal of the American Medical Association*, September 10, 2003)

Compliance with Lifestyle Recommendations to Lower Blood Cholesterol

The NHLBI National Cholesterol Education Program (NCEP) recommends therapeutic lifestyle changes (i.e., reducing dietary intake of saturated fat and cholesterol, increasing physical activity, controlling weight) as a first step toward reducing high blood cholesterol levels. An analysis of postmenopausal women participating in the WHI–OS indicates that many women are not complying with NCEP recommendations. Of the 13,777 participants who reported having been prescribed drug therapy for high cholesterol levels, only 20 percent had dietary habits (i.e., intake of total fat, saturated fat, and dietary cholesterol) that were in line with NCEP recommendations. Consistent with other studies, the WHI–OS found that women who smoked, were inactive, or had a higher body mass index were less likely to follow dietary guidelines. Better health promotion approaches are needed to help older women modify their lifestyles in order to reduce the burden of CVD. (*American Journal of Medicine*, October 1, 2002)

WHI: Future Plans

Although the hormone therapy clinical trials were stopped early, other WHI activities are continuing until their scheduled end in March 2005 (i.e., the clinical trials of low-fat diet and calcium/vitamin D supplementation and the WHI–OS). Hormone trial participants will receive additional monitoring (e.g., review of annual mammogram reports) through 2007. The NHLBI also is negotiating with WHI centers for continued followup of participants through a WHI Extension Study, which will run through 2010; volunteers will be asked annually to complete health forms. The NHLBI also plans to support additional research on a large biologic specimen repository collected through the WHI.

The NHLBI recognizes that data from the WHI constitutes an important scientific resource that should be made available, under appropriate terms and conditions consistent with the informed consent provided by individual participants, to the largest possible number of qualified investigators. A time schedule has been established for appropriate release of the data.

Other Findings Related to Postmenopausal Hormone Therapy

Women's Angiographic Vitamin and Estrogen (WAVE) Trial

Adding to the WHI findings with respect to primary prevention of CVD, results from the NHLBI-sponsored WAVE trial indicate that postmenopausal hormone therapy is also not beneficial for secondary prevention. WAVE randomly assigned more than 400 postmenopausal women with CHD to receive hormone therapy or a placebo and high doses of vitamins C and E or a placebo. Angiograms were performed when women entered the study and approximately 3 years later to evaluate the extent and progression of coronary artery blockages. Researchers analyzed the results using a ranking system that incorporated both clinical events (e.g., heart attack, death) and angiographic changes. They found, much to their surprise, that the death rate was highest among women who took hormones and vitamins, and lowest among women who took placebos. Furthermore, participants taking hormones and vitamins experienced as much or more progression of their coronary artery blockages as those on placebos. These findings add to the growing body of evidence that postmenopausal hormone therapy is not helpful in preventing or treating heart disease and may, indeed, be harmful. (*Journal of the American Medical Association*, November 20, 2002)

Another analysis of WAVE data considered the effects of postmenopausal hormone therapy on coronary atherosclerosis in women with abnormal glucose tolerance (AGT, defined as diabetes or impaired fasting glucose) versus women with normal glucose tolerance. After 3 years of followup, the study found that hormone therapy accelerated progression of existing blockages in all the women, and appeared to enhance atherosclerosis development in previously non-diseased artery segments in the women with AGT. These findings demonstrate that hormone therapy use is not warranted in diabetic women. (*Circulation*, July 13, 2004)

Trends in Use of Postmenopausal Hormone Therapy

The recent evidence that postmenopausal hormone therapy should not be used for prevention of chronic diseases has had a rapid impact on prescribing behavior in the United States. An analysis funded by the NHLBI and the Agency for Healthcare Research and Quality found a dramatic change in hormone prescribing in the aftermath of the July 2002 publication of findings from the WHI and the industry-sponsored Heart and Estrogen/Progestin Replacement Study (HERS) II. Specifically, researchers documented a decline of 66 percent for Prempro® and 33 percent for Premarin® between the periods of January to June 2002, and January to June 2003. For a broader perspective, investigators examined trends from 1995 to 2003. Prescriptions for hormone therapy, which had been on the rise for 2 decades, increased from 58 million in 1995 to 90 million in 1999, where they remained stable until June 2002. At that time, approximately 15 million American women were using hormone therapy. Assuming the prescription rates observed in July 2003 remain stable throughout the year, it was estimated that only 57 million prescriptions were dispensed in 2003, nearly the same number as seen in 1995. These data underscore the need for evidence-based results and the value of

translating those results into clinical practice. (*Journal of the American Medical Association*, January 7, 2004)

Results from the Women's Ischemia Syndrome Evaluation (WISE) Study

The WISE is a multicenter study initiated by the NHLBI in 1996 to evaluate ischemic heart disease in women. It focuses on three areas of particular relevance to heart disease in women: 1) optimizing symptom evaluation and diagnostic testing for ischemic heart disease; 2) understanding the biological mechanisms responsible for myocardial ischemia in the absence of epicardial coronary artery disease (CAD); and 3) evaluating the influence of reproductive hormones on heart disease symptoms and responses to diagnostic tests. Secondary objectives of WISE are to develop safe and cost-effective diagnostics for evaluating women with suspected ischemic heart disease, to determine the frequency of myocardial ischemia in the absence of significant epicardial coronary stenosis, and to determine the frequency of nonischemic or noncardiac chest pain. In fiscal year 2001, the NHLBI extended followup of WISE to study the long-term prognostic value of new tests developed in earlier phases of the program, to develop sex-specific outcome models to evaluate the prognostic value of female reproductive variables, and to maintain a WISE database and infrastructure. Some of the results published by the WISE investigators in 2004 are described below.

Low Hemoglobin Levels and Outcomes in Women with Chest Pain

Several studies have shown that low hemoglobin (Hgb) levels are associated with increased CVD-related morbidity and mortality in patients who suffer a heart attack or who have heart failure. A recent WISE study investigated whether low Hgb levels are also associated with adverse cardiovascular outcomes in women who experience chest pain. Results showed that women with chest pain who have low Hgb levels are more likely than women with normal Hgb levels to die, suffer a heart attack, develop heart failure, suffer a stroke, or experience other adverse cardiovascular events. Surprisingly, in this study the Hgb levels associated with adverse events were only mildly to moderately low by current standards. Also unexpected was the finding that low Hgb levels were a better predictor of adverse cardiovascular events than were most traditional risk factors such as smoking, hypertension, age, and family history of heart disease. The researchers also showed that markers of inflammation, which are a risk factor for CVD, were higher in the women with low Hgb. Researchers are now focusing on understanding why low Hgb levels are linked to poorer outcomes, determining whether treatment to raise Hgb levels will improve outcomes, and determining the level of Hgb that should be defined as "high risk." (*Journal of the American College of Cardiology*, June 2, 2004).

Metabolic Syndrome and CAD

The metabolic syndrome—characterized by co-occurrence of abdominal obesity, low HDL cholesterol, elevated triglycerides, high blood pressure, and abnormal glucose—is thought to be an intermediate step in progression from normal glucose homeostasis to a diabetic state. Currently, the relationship between the metabolic syndrome, CAD, and risk of other adverse cardiovascular events is not entirely clear. To gain a better understanding of the usefulness of the metabolic syndrome as a predictor of CVD risk, the WISE investigators tested women to determine their metabolic status (normal, metabolic syndrome, or diabetic) and whether they had CAD. They then followed the women for 4 years and assessed the relationship between metabolic status, CAD, and risk of experiencing a major cardiovascular event. Results showed that the 4-year risk of experiencing such an event increases across the metabolic continuum from normal to diabetic—women with diabetes had the highest risk, women with a normal metabolic status had the lowest risk, and women with the metabolic syndrome had an intermediate risk of adverse cardiovascular events. The researchers looked at the results to determine the effect of the presence or absence of CAD. Interestingly, they found that the metabolic syndrome was associated with an increased risk for major cardiovascular events only in women with the syndrome who had CAD at the time of entry into the study. The result is consistent with previous observations that the risk associated with the metabolic syndrome is variable and suggests that measurement of both metabolic status and CAD provides

a better indicator of risk for future cardiovascular events risk than assessment of metabolic status alone. (*Circulation*, February 17, 2004)

Obesity and CVD Risk

The recent rise in obesity prevalence is a major public health concern because obesity is often associated with CVD risk factors, such as metabolic abnormalities (i.e., the metabolic syndrome, diabetes) and a lack of physical activity. Although obesity is also associated with CVD, controversy is growing over whether it is obesity itself that increases an individual's risk of CVD or the presence of the risk factors that often accompany obesity. The distinction is important because not all obese individuals have the metabolic syndrome or lead sedentary lifestyles. Two recent WISE studies evaluated the relationship between obesity and CVD risk.

In the first study, the researchers classified 780 of the WISE participants as normal, overweight, or obese, according to their body mass index, and as normal, metabolic syndrome, or diabetic, according to their metabolic status. After 3 years of followup, the risk of CVD in obese women with a normal metabolic status was relatively low. Conversely, normal-weight women who had the metabolic syndrome were at a relatively high risk for CVD. The authors concluded that metabolic status rather than being overweight or obese predicts future CVD. (*Circulation*, February 17, 2004)

A second study looked at whether physical fitness affects CVD risk. Interestingly, results showed that women with the highest self-reported physical fitness scores had the lowest risk of adverse cardiovascular events whether they were normal weight, overweight, or obese. In fact, obese women with a high fitness level were at lower risk than normal-weight women who were not fit. (*Journal of the American Medical Association*, September 8, 2004)

While the two studies suggest that metabolic factors and physical fitness are more important predictors of CVD risk than obesity alone, they also underscore the importance of controlling all modifiable risk factors in both normal and overweight women.

Serum Amyloid A and CVD Risk

A growing body of evidence suggests that inflammation—a process by which the body responds to injury—is associated with the development of CVD. Blood proteins whose levels increase during inflammation are now being used to develop tests for the presence of inflammation. WISE investigators recently evaluated one such protein, serum amyloid-a (SAA), to determine whether it might be useful in predicting which women would develop CAD and other forms of CVD. The results showed that SAA was moderately associated with development of CAD. They also showed that a high level of SAA was a good predictor of the 3-year risk of suffering an adverse cardiovascular event. Based on these results, SAA shows promise for helping doctors to identify women at high risk for CVD. (*Circulation*, February 17, 2004)

Coronary Vascular Dysfunction and CVD Risk

Normal coronary arteries dilate in response to the chemical acetylcholine. Impaired coronary reactivity to acetylcholine is an indication of vascular dysfunction that is believed to be a precursor to atherosclerosis and CAD. To determine whether coronary vascular dysfunction predicts adverse outcomes in women, the WISE investigators measured coronary artery reactivity in 163 study participants who had been referred for clinically indicated coronary angiography. After assessing arterial response to acetylcholine, the researchers followed the women for an average of 2 years to ascertain subsequent cardiovascular status. Results showed that impaired coronary vascular response to acetylcholine was independently linked to cardiovascular events, such as heart attack or coronary revascularization. The finding is striking because most of the women in the study did not have significant angiographic CAD and were, therefore, at relatively low risk for imminent coronary events. (*Circulation*, February 17, 2004)

Gender Differences in Heart Failure

Trends in Incidence and Survival

Investigators used long-term data from the Framingham Heart Study to assess temporal trends in incidence of heart failure and survival after its diagnosis. The analysis revealed that, over the past 50 years, incidence of heart failure decreased by about one-third among women, whereas it changed very little among

men. The researchers hypothesize that the availability of better drugs for controlling high blood pressure, the most prominent cause of heart failure in women, might explain why fewer women are developing the disease. The study also found that improved survival after onset of heart failure has occurred in both genders—on average, age-adjusted death rates for women and men diagnosed with heart failure dropped 12 percent during each decade between 1950 and 1999. Further research is needed to determine the factors underlying this trend. (*New England Journal of Medicine*, October 31, 2002)

Remodeling Following Heart Attack

A number of studies have showed that women with symptomatic heart failure tend to fare better than men, but the reasons for this gender difference have been unclear. A recent study of patients undergoing cardiac transplantation for end-stage heart failure has shed light on this issue. The researchers found that men and women undergo quite different changes in the morphology of the heart muscle—a process known as remodeling—following a heart attack. Men developed much larger hearts (caused only in part by increased left ventricle size) than women, and their individual heart cells also were larger. The larger cells were found throughout the hearts of men rather than just in tissue near the area damaged during the heart attack, and the researchers concluded that damage during a heart attack triggers remodeling in distant cells. Further understanding of the gender-specific remodeling process may provide a key to developing new approaches to prevent development of heart failure in heart attack survivors. (*Journal of the American College of Cardiology*, January 15, 2003)

Use of Digoxin Therapy for Women

In 1997, the NHLBI-supported Digitalis Investigation Group reported the findings of a controlled clinical trial of digoxin therapy in patients with heart failure and depressed left ventricular function. Although digoxin did not confer a mortality benefit, it reduced the rate of hospitalization during the 3-year follow-up period. A subsequent analysis sought to determine whether gender differences existed in response to digoxin therapy. It revealed an increased risk of death for the subgroup of women receiving digitalis compared with women assigned to the placebo arm of the trial. Moreover, women experienced a smaller digoxin-associated reduction in hospitalization for worsening heart failure than men. These findings underscore the importance of examining gender differences in treatment efficacy, and suggest that re-evaluation of the appropriate use of digoxin therapy in women is warranted. (*New England Journal of Medicine*, October 31, 2002)

Plasma Homocysteine and Risk of Heart Failure

Researchers have found the first evidence that increased plasma levels of homocysteine, a known risk factor for CHD and stroke, also may raise risk of developing heart failure. The relation between heart failure and homocysteine did not vary with age, systolic blood pressure, or use of diuretic or cholesterol-lowering drugs. However, gender differences were found—in women, progressively higher levels of homocysteine were correlated with higher heart failure rates even when homocysteine was below the average level for women, whereas in men the relation became apparent only at above-average levels. Although the connection between failure and homocysteine level and the differences in risk for men and women need to be corroborated by other studies, these findings may ultimately have public health implications, given the considerable morbidity, mortality, and economic burden associated with heart failure. (*Journal of the American Medical Association*, March 12, 2003)

Other Findings Related to CVD Risk and Its Modification

Predictors of Future CVD in Young Women

Results from a study begun in 1967 demonstrate that it is never too early to pay attention to heart health. Researchers from the Chicago Heart Association Detection Project found that young women who had two or more major CVD risk factors (diabetes, high blood pressure, an unhealthy cholesterol profile, BMI >25.0, smoking) when they joined the study were less likely to be alive in 2001 than counterparts who had none of the risk factors. Specifically, the higher-risk women were seven times more

likely to have died of CHD, six times more likely to have died of CVD, and more than twice as likely to have died of any cause. Although the relation between CVD risk factors and decreased longevity had been established for young adult men and middle-aged men and women, the Chicago project is the first to measure the link for young women. Coupled with the observation that only 20 percent of the women in this cohort could be classified as "low risk," these findings underscore the urgency of establishing heart-healthy habits among women early in life. The NHLBI is currently supporting two clinical trials in adolescent girls—addressing physical activity and weight gain, respectively—that are expected to guide enhanced CVD prevention efforts in young women. (*Journal of the American Medical Association*, October 6, 2004)

CVD Screening Tool

Exercise testing, often performed using a treadmill, is a valuable screening tool for identifying potential heart problems in apparently healthy men, but its usefulness in women has been questioned. Long-term followup of the NHLBI Lipid Research Clinical Prevalence Study has shed new light on this issue, revealing that the test parameters having prognostic significance in women are somewhat different from those in men. Specifically, an electrocardiographic finding of ST-segment depression—which indicates low blood flow to the heart muscle and is an ominous sign in men—was found to be unrelated to increased risk in women. However, two measures of cardiovascular fitness—exercise capacity and heart rate recovery—proved to be quite useful for predicting risk in women. The findings have particular public health significance because the fitness measures presaged CVD deaths 20 years later even among women who were considered to be at low risk for heart disease. Because approximately two-thirds of women who die suddenly of CVD have no previous symptoms, a straightforward, noninvasive approach to identifying asymptomatic women who may benefit from aggressive primary prevention could save many lives. (*Journal of the American Medical Association*, September 24, 2003)

C-Reactive Protein Level and CVD Risk

Based on recent evidence suggesting that serum levels of C-Reactive Protein (CRP)—an indicator of inflammation—independently predict risk for CVD, doctors have begun to incorporate assessment of CRP into clinical practice. However, many questions remain about the significance of CRP measurements, particularly at very high or very low levels, or in the context of other CVD risk factors. Recent findings from the NHLBI-supported Women's Health Study (WHS) have shed light on some of these issues.

Individuals with the metabolic syndrome are at increased risk for developing diabetes and CVD, and many of the syndrome's defining characteristics are associated with increased C-reactive protein (CRP) levels. WHS researchers investigated whether measuring CRP levels in women with the metabolic syndrome would provide additional information about individual risk of CVD. They found that CRP levels at the beginning of the study were strongly related to severity of the metabolic syndrome (i.e., CRP levels were lowest in women who had none of the abnormalities associated with metabolic syndrome and highest in women who had all of them). Followup 8 years later revealed that CRP levels added clinically relevant prognostic information concerning future CVD risk among women with and without the metabolic syndrome. For example, in the subgroup of women who had three characteristics associated with the metabolic syndrome, those with CRP levels >3.0 mg/L had nearly twice the rate of cardiovascular events of those with lower CRP levels. The results suggest that CRP levels can be useful in refining assessments of cardiovascular risk in women. (*Circulation*, January 28, 2003)

Many researchers have speculated that hypertension is part of an inflammatory disorder, and findings from the WHS have added support for this hypothesis. Investigators found that CRP levels at the beginning of the study were significantly related to the likelihood of developing hypertension during the follow-up period, which averaged 7.8 years. This relation held even for women who had no traditional CVD risk factors or very low baseline blood pressures. These results provide further evidence that inflammation may play a role in the development

of hypertension and also indicate that CRP may be useful in predicting a person's risk of hypertension, as well as heart attack and stroke. (*Journal of the American Medical Association*, December 10, 2003)

As routine measurement of CRP by community physicians has become more common, questions have emerged about the predictive value of very high or very low CRP levels. For instance, concern exists that a low CRP level might give patients a false sense of security, especially when other risk factors are present. Conversely, a very high level might represent a temporary response to an acute condition rather than a predictor of future risk. A new analysis of WHS data indicates that the predictive value of high-sensitivity CRP is linear across a full range of values, even after other risk factors are taken into account. The researchers concluded that CRP can be used to assign individuals to low-, moderate-, or high-risk categories for future cardiovascular events. (*Circulation*, April 27, 2004)

Moderate Physical Activity Promotes Weight Loss As Well As Intense Exercise

Women trying to lose weight can benefit as much from moderate physical activity as from intense workouts. This conclusion came from a clinical trial involving 201 overweight but otherwise healthy women, 21 to 45 years of age, who were provided with meal plans and instructed to limit their food intake to 1,200 to 1,500 kilocalories per day. Participants also were assigned randomly to one of four physical activity regimens that varied by intensity (moderate versus vigorous exercise) and duration (2 ½ to 3 ½ versus 3 ½ to 5 hours per week). Women in all four groups lost a significant amount of weight—13 to 20 pounds—and maintained their weight loss for a year. They also improved their cardiorespiratory fitness. (*Journal of the American Medical Association*, September 10, 2003)

Women's Heart Disease Awareness Campaign

The Heart Truth campaign, with its Red Dress icon and slogan—Heart Disease Doesn't Care What You Wear: It's the #1 Killer of Women—is raising awareness among women of their risk of heart disease and motivating them to take steps to reduce it. Groundbreaking partnerships with the fashion industry and corporate America have greatly expanded coverage of the campaign since it was launched in September 2002. The Red Dress symbol and information about heart disease are appearing in homes across America through everyday products, such as cereal boxes and fashion magazines. Although they may be somewhat unconventional health education approaches, these partnerships are enabling the campaign to reach millions of women.

The Heart Truth Road Show also delivered information directly to women throughout the nation. The traveling exhibit, which featured red dresses from America's leading fashion designers, provided health screenings to 4,000 women and information to more than 86,000 individuals during its five-city tour. The campaign team also addressed the interests of state and local government agencies, health professional organizations, and community groups by offering them opportunities to implement activities in their communities and participate in national events. One such event is National Wear Red Day, which encouraged individuals to wear red to show their support for raising awareness that far more American women die of heart disease than of any other cause.

Building on its strong partnership base, the campaign continues to expand its outreach activities, especially with women of color, to ensure that women know The Heart Truth and take their heart health seriously. The Heart Truth is being conducted in partnership with the American Heart Association, the Office on Women's Health of the U.S. Department of Health and Human Services, WomenHeart–the National Coalition for Women with Heart Disease, and other organizations committed to the health and well-being of women.

Hypertension in Pregnancy

NHLBI Working Group

In 2003, the NHLBI Working Group on Research in Hypertension During Pregnancy published a summary of what is known about pregnancy-related hypertension and recommendations for research to address key unanswered questions. Although much has been learned about preeclampsia during the past decade, gaps remain in the knowledge necessary to direct therapeutic strategies. For

example, because oxidative stress is a biologically plausible contributor to the disorder, a clinical trial of antioxidant therapy for prevention is warranted. The trial should be complemented by research to increase understanding of the genetics and pathogenesis of preeclampsia. Recognizing that chronic hypertension in pregnancy is becoming increasingly common as women delay childbearing, the group also recommended clinical research to determine the best choice of antihypertensive medication in terms of blood pressure control, fetal growth and safety, and genetic variation in response to therapy. (*Hypertension*, March 2003)

Role of Neutrophils and Inflammation in Preeclampsia

Recent evidence indicates that neutrophils—the bacteria-eating cells of the immune system—may play a role in hypertension, proteinuria, and edema during preeclampsia. Building on knowledge that neutrophils are activated during pregnancy and are capable of damaging host tissues, researchers looked at interactions between neutrophils and blood vessels from pregnant women with preeclampsia, healthy pregnant women, and nonpregnant women. Compared with the vascular smooth muscle tissue of healthy pregnant or nonpregnant women, tissue from women with preeclampsia showed evidence of inflammation and expressed significantly more of a molecule that attracts and activates neutrophils. Neutrophils were found in a greater percentage of vessels from preeclampsia patients, and in greater numbers within their blood vessels. Furthermore, additional neutrophils had infiltrated spaces within tissues surrounding the vessels of women in the preeclampsia group, a finding not observed in tissues from the other groups. Taken together, these results—the first to find vascular smooth muscle inflammation and neutrophil infiltration in women who have preeclampsia—offer a possible explanation for the endothelial and vascular smooth muscle dysfunction that characterizes preeclampsia. (*Hypertension*, July 2004)

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare and devastating lung disease that primarily affects young women. Lung function worsens steadily in LAM patients because of overgrowth of smooth muscle cells and formation of numerous cysts throughout the lungs. Supplemental oxygen may be useful in alleviating the hypoxemia, or low blood oxygen, associated with LAM in its early stages, but as the disease progresses, lung transplantation often becomes the only treatment option. In some patients, loss of lung function occurs gradually, but in others disease progression is rapid, necessitating transplantation after only a few years. Previously, lung diffusion studies and measurements of forced expiratory volume were routinely used by clinicians to guide them in treatment of LAM patients. Recently, however, NHLBI-supported intramural investigators used cardiopulmonary exercise testing (CPET) to evaluate lung function in 217 LAM patients. The researchers found that CPET was a better predictor of hypoxemia than the usual diffusion and expiratory volume tests, which are done on resting patients. During CPET, hypoxemia occurred in some patients who otherwise had normal diffusion and expiratory volume tests. The CPET method of evaluating lung function in LAM patients appears to be a better predictor of overall lung function and may be useful in determining which patients are likely to need transplantation. (*American Journal of Respiratory and Critical Care Medicine*, December 15, 2003)

Sarcoidosis

Sarcoidosis is a systemic disease involving multiple organ systems that appears to affect women disproportionately. The NHLBI sponsored a working group on Future Directions in Sarcoidosis Research in August 2002. The panel recommended developing a tissue bank to collect lung and other affected tissues, identifying genetic factors involved in sarcoidosis, studying the immunopathogenesis of sarcoidosis in relevant animal models and in human tissue, improving the management of patients with sarcoidosis, and conducting randomized controlled trials using new therapies for sarcoidosis. The NHLBI is working with the scientific community to implement the recommendations. (*American Journal of Respiratory and Critical Care Medicine*, September 2004)

Smoking Cessation and Lung Health

Cigarette smoking is a leading cause of chronic obstructive pulmonary disease (COPD), so smokers who develop COPD are strongly urged to quit. The NHLBI Lung Health Study of middle-aged smokers with mild-to-moderate airflow obstruction found that in the first year after quitting smoking, women's lung function improved more than twice as much as mens. Among participants who quit smoking, improved lung function remained greater for women than for men throughout the duration of the 5-year study. While both men and women benefit from quitting smoking, results of the study should be especially encouraging to women who are considering kicking the habit. (*American Journal of Epidemiology*, June 1, 2003)

Bleeding Disorders in Women

The NHLBI is increasing its efforts to improve diagnosis and treatment of bleeding disorders in women, which are a significant source of illness and diminished quality of life. A panel of experts convened in June 2004 identified research areas needing additional attention, and the institute is working with the scientific community to address them. Additionally, the NHLBI, in consultation with the American Society of Hematology, has formed a working group to examine the current science in the area of von Willebrand disease, a bleeding disorder that affects women, and develop science-based clinical recommendations for its diagnosis, treatment, and management. The audience for the recommendations is practicing primary care physicians, including general practitioners, family practitioners, internists, gynecologists, and pediatricians. The guidelines are scheduled for completion by December 2005, and they will be widely disseminated by the NHLBI, the American Society of Hematology, and other interested groups.

Lupus and Atherosclerosis

Although systemic lupus erythematosus (SLE) has been linked to an increased risk of CAD and myocardial infarction, the association between SLE and atherosclerosis is not well understood. Two groups of NHLBI-supported investigators recently studied the prevalence of atherosclerosis in SLE patients, compared with matched controls. The first group used ultrasonography to measure carotid artery atherosclerosis, while the second used computed tomography (CT) to assess coronary artery calcification. Results from the ultrasonography studies indicated that atherosclerosis develops earlier in patients with SLE, while the CT results indicated that the prevalence of coronary-artery atherosclerosis is higher and has an earlier age of onset in patients with SLE. These results suggest the need for earlier clinical evaluation and aggressive treatment for SLE patients in order to reduce the risk of atherosclerosis. (*New England Journal of Medicine*, December 18, 2003)

Initiatives

Request for Proposals (RFPs)

- **Field Centers for the Women's Health Initiative Extension**
  The NHLBI issued this RFP to extend the existing Women's Health Initiative (WHI) Field Center contracts to ensure continued health surveillance of the WHI hormone therapy trial participants through September 2007. During the additional $2^1/_2$ years of participant followup, health outcomes will be ascertained and mammography data will be collected. (NHLBI-WH-04-17)

- **Renewal of the Jackson Heart Study**
  These RFPs provide funding for the Jackson Heart Study (JHS) through FY 2009. Expansion of the JHS, a large study of CVD risk in African American women and men in Jackson, Mississippi, will enable support for additional clinical examinations and data collection. It will also sustain and enlarge the Jackson-area community health education component, which uses data derived directly from the JHS cohort to develop and disseminate practical, up-to-date information on reduction of risk factors, practice of healthy lifestyles, and adherence to proven risk-reducing therapies. (NHLBI-04-25 and NHLBI-04-26)

Request for Applications (RFA)

- **Granulomatous Lung Inflamation in Sarcoidosis**
  Based on recommendations of the NHLBI working group on future research directions in sarcoidosis, the NHLBI issued this RFA to identify the innate and/or adaptive immune pathways that affect lung lymph nodes or tissue in early disease, and to study the immunopathogenesis of granulomatous inflammation similar to that found in sarcoidosis so that therapeutic targets for clinical trials can be identified. (RFA-HL-04-009)

Program Announcements (PAs)

- **Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases**
  The NHLBI issued this PA with the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Cancer Institute, the National Center for Complementary and Alternative Medicine, the National Institute on Biomedical Imaging and Bioengineering, and the National Institute of Nursing Research to stimulate research on the biology of the lymphatic system, to characterize the pathophysiologic mechanisms that cause the disease, to develop new methods for quantitating and imaging lymph flow, to discover new therapeutic interventions, and to determine the safety and efficacy of complementary and alternative therapies. Lymphedema, which is characterized by abnormal fluid accumulation and swelling, is a particular concern of women who have surgery or radiation treatment for breast cancer. (PA-04-071)

- **Exploratory and Developmental Research Grants for Investigations in Rare Diseases (R21)**
  Using the R21 funding mechanism, which supports exploratory and developmental research projects, the NHLBI and the NIH Office of Rare Diseases issued this PA to encourage innovative approaches to understanding, treating, and preventing rare diseases in the areas of heart, lung, and blood and sleep disorders, such as LAM and sarcoidosis, both of which disproportionately affect women. (PA-03-171)

Conferences and Workshops

- **NHLBI Workshop on Women and Ischemia Syndrome Evaluation (WISE): Diagnosis and Pathophysiology of Ischemic Heart Disease**
  October 2-4, 2002

- **Women with Bleeding Disorders Working Group**
  June 2, 2004

Health Disparities among Special Populations of Women

While heart disease and stroke remain the first and third most common causes of death of all Americans, African Americans suffer disproportionately from these diseases. For example, in Mississippi the age-adjusted CVD mortality for African American women is 75 percent higher than for white women, and African American men have rates 47 percent higher than those of white men. To investigate disparities in CVD prevalence, severity, and mortality among African Americans, the Jackson Heart Study (JHS) was initiated in 1998. The project has enrolled 5,500 African American women and men living in the Jackson, Mississippi area, and it will continue through 2009. The JHS is uniquely positioned to identify factors that influence the development and worsening of CVD in African Americans, with an emphasis on manifestations related to hypertension such as CAD, heart failure, stroke, peripheral arterial disease, and renal disease.

Gender Analysis

As noted under Accomplishments, researchers recently identified a number of gender differences with regard to heart failure mortality, survival, risk, and response to treatment.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

The National Human Genome Research Institute (NHGRI) led the National Institutes of Health's (NIH) contribution to the International Human Genome Project (HGP). With the achievement of its final goal, the finished sequence of the human genome in April 2003, this project was successfully completed ahead of schedule and under budget, and has already begun to change the way we address research on women's health.

In October 2004, the International Human Genome Sequencing Consortium, led in the United States by the NHGRI and the Department of Energy, published an analysis of that finished human genome sequence in the journal, *Nature*. This analysis reduces the estimate of the number of human protein-coding genes from 35,000 to only 20,000 to 25,000—a surprisingly low number for our species, considering that only a decade ago most scientists thought we had over 100,000 genes.

The NHGRI has moved forward into the genomic era with a wide range of powerful new extramural research initiatives that will accelerate genome research and its application to human health. The NHGRI also supports research to study the ethical, legal, and social implications of genomic research, known as "ELSI." The ELSI program at the NHGRI is the largest supporter nationwide of ELSI research. As well, in its Division of Intramural Research (DIR) scientists are using the techniques and tools produced by the HGP—and developing new ones—to study the fundamental mechanisms of inherited and acquired genetic disorders, including many disorders that are more prevalent in women, to lead ultimately to improved diagnostic, prevention, and treatment strategies.

Accomplishments

The Role of the BRCA1 and BRCA2 Gene in the Pathogenesis of Breast Cancer

The work of a group of NHGRI researchers is focused on defining changes in the genes that underlie inherited susceptibilities to common diseases, such as cancer and birth defects. Currently under investigation are the inherited breast and ovarian cancer genes, BRCA1 and BRCA2. The biological function of these proteins is currently unknown. Previously, NHGRI researchers discovered which proteins specifically interact with BRCA1. In the past year they have found that BRCA1 is important for controlling the expression of other genes and plays a role in DNA repair. Recent experiments have revealed that BRCA1 appears to help in the process of recognizing and eliminating cells that may progress to form tumors. It is now known that the increase in breast, ovarian, and prostate cancer risk associated with genetic variants in these genes is due to a failure of these mutated proteins to function in the DNA repair pathway. NHGRI researchers are using yeast cells as an experimental model to test the functional consequences of mutations found in humans, and have also developed a system for identifying proteins that interact with BRCA1. An increased understanding of the BRCA1 and BRCA2 genes will lead to improved diagnostic procedures and possible preventative therapies.

Parent Communication of BRCA1/2 Test Results to Children

One of the primary motivations for parents to participate in BRCAI/2 testing is to find out about their minor children's risk of developing cancer. However, parents often report feeling distressed and conflicted about sharing this information with their youngsters once it is available. As few parents receive professional guidance in evaluating the potential risks and benefits of disclosure to children, parents may be prone to make ineffective decisions about communication that could lead to adverse psychosocial outcomes. As clinical genetic testing becomes increasingly more common, this presents an ethical challenge that needs to be better understood so that interventions to promote positive outcomes can be implemented. Through the ELSI program, the NHGRI is funding a prospective, longitudinal study to examine decisionmaking about disclosing a maternal BRCAI/2 test result to children and the psychosocial outcomes of parents' communication choices among tested mothers and non-tested fathers. This research aims to: 1) establish rates of mothers' disclosure of a BRCA1/2 test result to minor children and to identify the determinants of the decision

to disclose or not disclose; 2) evaluate the impact of BRCA1/2 test result and mother-father shared decisionmaking on parents' communication choices; and 3) evaluate the impact of BRCA1/2 test result communication decisions on psychosocial well being.

Genetic Epidemiology of Breast Cancer

NHGRI researchers are carrying out a collaborative linkage study of breast cancer families that do not have mutations in either the BRCA1 or BRCA2 genes to identify other genes that are involved in breast cancer. Collaborators in Finland, Sweden, and Iceland are working together with the NHGRI to add more families to the data set. Genotyping of several candidate regions and a genome-wide scan have been performed on these samples. Linkage analysis is ongoing and a paper was published in *PNAS* in early 2000 suggesting the possibility of an additional gene (BRCA3) relatively close to the BRCA2 locus. Fine mapping of this region is also ongoing to narrow in on this gene. Families that did not appear linked to BRCA1, BRCA2, or this novel BRCA3 locus have also been genotyped for a genome scan panel of marker loci. Several novel regions showed some evidence for linkage, suggesting additional genes related to the development of breast cancer, and the regions with the strongest evidence for linkage are currently being followed up with fine mapping studies. A paper detailing these results was published in 2004.

Functional Genomics of Cancer

One of the major problems in cancer biology is to define the aberrant pattern of gene expression in tumor cells and to relate this pattern to specific genomic alterations which occur during the development of tumors. To address this issue, a novel technology, DNA microarray hybridization, is being applied at the NHGRI to analyze the consequences of chromosome anomalies at the level of gene expression. Using a robotic device, it is possible to print thousands of DNA probes representing the complete genome on a single microscope slide. The ultimate goal of this project is genome-wide gene expression analysis. In this fashion, it is proving possible to profile individual diseases, and to determine the consequences of a given genetic alteration on gene expression. This technology is now being applied in model systems. Recent efforts of NGHRI scientists have applied this technology to pediatric cancers, adult sarcomas, melanoma, and breast cancers. They have been able to establish the potential of microarrays for the accurate diagnosis of pediatric cancers and for distinguishing estrogen receptor-positive breast cancers from receptor-negative tumors. Using data from laboratory models they have uncovered patterns of gene expression related to important clinical properties of cancers, such as estrogen sensitivity in breast cancer and metastasis in melanoma and osteosarcoma.

Outcomes of Education and Counseling for HNPCC Testing

Hereditary nonpolyposis colorectal cancer (HNPCC) is a hereditary cancer syndrome that includes cancer risks for colon, endometrial, ovarian, stomach, small intestine, gall bladder, urinary tract (kidney, bladder, ureters), brain and, rarely, pancreas. Woman in these families may have as high of risk for endometrial cancer as they do for colon cancer. NHGRI investigators are identifying factors influencing decisionmaking regarding genetic testing for HNPCC and the psychological and behavioral outcomes of the testing process. Those with a cancer meeting selection criteria or in a family with a known HNPCC mutation complete a baseline questionnaire assessing knowledge, expectations, mood, attitudes, perceived cancer risk, cancer worries, family relationships, spirituality, coping, and health beliefs. Participants are then provided with an educational/counseling session focused on HNPCC; the availability of genetic testing, its risks, limitations and potential benefits; and cancer screening recommendations for families with HNPCC. Participants are then presented with a choice of whether or not to undergo genetic testing. Those choosing genetic testing undergo a separate informed consent and are reassessed through telephone questionnaires at 6 and 12 months following risk notification or the decision not to undergo testing. For those receiving genetic

test results, notification occurs in person along with discussion of available surveillance options. Follow-up counseling and support are provided for all individuals participating in the study.

NHGRI investigators are currently analyzing data and writing a manuscript that examines endometrial/ovarian cancer screening before and after genetic counseling and testing in women within HNPCC families with identified mutations.

Prophylactic Mastectomy: The Patient Experience

The NHGRI is funding research on the psychosial outcomes of prophylactic mastectomy (PM) through the ELSI program. PM has been shown to reduce the risk of breast cancer 90 percent in women at high and moderate risk, but its use is limited by low acceptability. Researchers caution that this is a highly personal decision, but patients and providers have little data about psychosocial outcomes of PM. Project goals are: 1) to describe the self-perceived benefits of PM and the physical, emotional, and interpersonal impacts; 2) to describe the impact of cancer family history and family communication on decisionmaking for and outcomes of PM; 3) to utilize case comparisons to assess the relative influence of medical, psychological, and family factors in determining positive or adverse outcomes of PM; and 4) to produce a monograph based on the qualitative analysis and emphasizing first-person narratives for use by women considering PM and as a tool for health care providers in advising their patients. This project will analyze interview narratives from a previously funded research project on psychological consultation needs of women considering or recovering from PM. A monograph utilizing the narratives and organizing them into user-friendly topic areas for patients will be developed. Reports for providers will also hopefully enhance advice to patients. Future research may assess utility of this material for women considering PM and for health care providers. Data from the project will inform hypothesis formation for future studies of PM.

Initiatives

The U.S. Surgeon General's Family History Initiative

The U.S. Surgeon General's Family History Initiative was launched on November 8, 2004 with the NHGRI as the lead collaborating federal agency. The purpose of this national public health campaign is to: increase the awareness of the American public and their health professionals about the importance of family history in health; provide tools to gather, understand, evaluate, and use family history to improve health; give health professionals tools to communicate with patients about family history; and increase genomics and health literacy. In 2004, two of the six diseases on which the initiative focused are of tantamount importance to women: breast cancer and ovarian cancer. A web-based and print tool, *My Family Health Portrait*, was developed in both English and Spanish to facilitate collection of family history data. To date, the initiative has been highlighted in more than 1,000 media stories and over 170,000 copies of the tool have been distributed via the world wide web and in paper form. This initiative is intended to be an annual event. For more information see *www.hhs.gov/familyhistory*.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases (NIAID) stands at the forefront of scientific research on a number of diseases that threaten the survival and quality of life of millions of people. The NIAID conducts and sponsors research focused on the diagnosis, treatment, and prevention of infectious diseases, as well as disorders of the immune system. Many of these diseases and disorders adversely affect women, including the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), and other sexually transmitted infections (STIs). The NIAID also addresses immune-mediated

diseases, including asthma and allergic diseases, and the immune-mediated rejection of transplanted solid organs, tissues, and cells.

In a continual response to the global prevalence of HIV/AIDS, and the frequency of heterosexual and perinatal transmission, the NIAID continues its commitment to support studies on HIV/AIDS in women. Ongoing natural history cohort studies and HIV/AIDS clinical trial networks have expanded their research on HIV/AIDS to investigate the etiology and pathogenesis of HIV/AIDS in women; the effectiveness of topical microbicides; and other promising approaches to decrease sexual transmission and improve treatment of HIV/AIDS in women.

The NIAID also supports perinatal AIDS-related research, and furnishes necessary information to: 1) design clinical trials for HIV/AIDS-infected pregnant women and children; 2) improve methods for detecting maternal–fetal retroviral transmission in human and animal models; and 3) prevent HIV/AIDS transmission from pregnant mothers to their babies. Based on preclinical research, NIAID is evaluating new therapies and approaches for the prevention of perinatal transmission, both domestically and internationally. Through the Pediatric AIDS Clinical Trials Group (PACTG), which is co-funded by the National Institute for Child Health and Human Development (NICHD), the NIAID continues to evaluate treatments for HIV/AIDS-infected children and adolescents.

STIs are critical global and national health priorities because of the devastating impact on women and infants, and the interrelationships with HIV/AIDS. STIs and HIV are linked by biological interactions and infections occurring in the same populations. Infection with certain STIs can increase the risk of HIV acquisition and transmission, as well as alter the course of disease progression. Recent studies indicate that the more prevalent non-ulcerative STIs (chlamydial infection, gonorrhea, bacterial vaginosis, and trichomoniasis), as well as the ulcerative diseases (genital herpes, syphilis, and chancroid), increase the risk of HIV transmission by at least two- to fivefold. In addition, STIs can cause long-term health problems, particularly in women and infants. Some of the sequelae of STIs include: pelvic inflammatory disease (PID); infertility; fetal wastage; low birth weight; congenital/perinatal infection; chronic conditions, such as neurosyphilis, tubal, or ectopic pregnancy; cervical cancer; increased risk of HIV infection; and perinatal or congenital infections in infants born to infected mothers.

In summary, the NIAID is continuing its activities in these diverse, but interrelated, areas of investigation, building on past findings and exploiting new scientific opportunities as they arise. The Office of Special Populations and Research Training (OSPRT), NIAID, is the coordination point for reporting the NIAID's research on women's health. This report provides an overview of the major accomplishments and initiatives within the institute that address women's health research.

Accomplishments

Infectious Diseases

Acquired Immunodeficiency Syndrome (HIV/AIDS)

The number of HIV-infected women in the United States is steadily growing. The epidemic among women began expanding in the mid-1980s, and its effects are being felt as more HIV-infected women develop AIDS. Women develop different HIV-related complications than men, such as recurrent yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, human papillomavirus infections, cervical tumors, and vulvar and vaginal carcinomas.

The NIAID fosters research on: 1) the natural history of HIV/AIDS disease in women; 2) the mechanisms of HIV/AIDS infection in women; 3) the virologic, immunologic, and hormonal factors that play a role in HIV/AIDS acquisition and disease progression in women; 4) the impact of new drugs on HIV/AIDS disease; and 5) the role of substance abuse, sexual behavior, and psychosocial factors.

The NIAID is studying the unique features of HIV/AIDS in women through two cohort studies: the Women's Interagency HIV Study (WIHS) and the Women and Infants Transmission Study (WITS). The WIHS is a multicenter, prospective cohort study established in August

1993 to study the natural history of HIV infection in women. It conducts investigations of biological and psychosocial aspects of HIV infection in women. Launched in 1990, the WITS studies the pathogenesis of disease progression in women and children, many who are on therapy, and evaluates the factors related to perinatal HIV transmission and disease progression in women and children, and adolescents females as some of these children mature to adolescence.

Clinical protocols are either underway or planned to address woman-specific treatment research questions. These studies have been conducted through three NIAID-supported clinical research mechanisms: 1) the Adult AIDS Clinical Trials Group (AACTG), 2) the Pediatric AIDS Clinical Trials Group (PACTG), and 3) the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). Each of these networks is committed to ensuring the inclusion of HIV-infected women in trials; conducting research on HIV-associated conditions that specifically affect non-pregnant and pregnant women; and identifying real and potential barriers to the recruitment and retention of women into clinical trials.

Within the Adult ACTG there is a Women's Health Committee formed to optimize the design, conduct, and analysis of clinical trials, and to maximize the recruitment and retention of women into clinical trials. This committee strives for a goal of at least 20 percent female enrollment in antiretroviral-naïve trials, and at least 15 percent in recovery and opportunistic infection trials to learn more about whether there are gender differences in treatment and response.

The FY 2003 figures for women in therapeutic clinical trial networks are as follows: Adult ACTG –19 percent; Pediatric ACTG – 54 percent; and CPCRA – 23 percent.

Currently, a total of 3,768 HIV-infected and -uninfected women are enrolled in the WIHS. Of those, 57 percent are African American, while more than 25 percent are Hispanic. Currently, WITS has enrolled a total of 438 women, 42.2 percent of whom were African American, while 48.9 percent were Hispanic.

NIAID scientists continue to study HIV epidemiology and transmission in collaborative studies of high-risk groups in Uganda, Congo, Zambia, Zimbabwe, South Africa, India, China, and the United States. Many important findings have resulted from this ongoing research. For example, scientists examined the effects of sexually transmitted infections on the dynamics of HIV-1 disease in a Ugandan cohort. These investigators examined HIV-1 viral load in this cohort containing patients with established HIV infection and patients with recently acquired infection. HIV viral loads were significantly higher in patients with genital ulcer disease and past infections with HSV2.

In 2000, the NIAID established two global research networks for HIV vaccine and prevention research. The HIV Vaccine Trials Network (HVTN) develops and tests preventive HIV vaccines, and the HIV Prevention Trials Network (HPTN) explores alternative measures, besides AIDS vaccines, that may be able to block or reduce infection with HIV. The HVTN and HPTN strengthen NIAID's capability to discover new and better measures to protect people, especially women and children, from HIV infection. Other accomplishments include:

Therapeutic Research

The PACTG continues in its 5-year award, made in March 2002. The network has emphasized a greater focus on both adolescent research and international pediatric research with collaborations with other networks, such as the AACTG and HPTN. The PACTG, in conjunction with the Women's Health Committee of the AACTG, have developed a scientific agenda to promote research in the area of gender- and sex-specific research in HIV/AIDS.

The Women's Health Committee of the Adult AIDS Clinical Trials Group primary mission is to support the work of the Research Agenda Committees within the AACTG to develop strategies for the prevention and treatment of HIV disease and the related complications in women, and to determine the unique HIV pathogenesis in women. The committee serves as a link between the PACTG and the AACTG for antiretroviral therapy (ART) clinical trials. It also serves in the same capacity with HPTN, ATN, and HVTN to facilitate the evaluation of research questions relevant to women. The AACTG

has the following scientific accomplishments related to women's health in HIV disease, gender and pharmacology, and complications of HIV disease:

HIV Disease

A5001, A5077, A5095, and A5142: Viral dynamic studies of blood and non-blood compartments are underway to examine the potential sex/gender differences and responses in virologic and immunologic responses to therapy. In A5077, a longitudinal study, several sex differences in blood and non-blood compartments were observed. More male subjects than women subjects had detectable HIV-1 RNA in genital fluids.

Studies regarding prevalence and correlates of hormonal contraception use by HIV-1-positive women are underway. Several collaboration studies with the PACTG to examine the pharmacokinetics of contraceptives in the setting of therapy HAART are ongoing.

In PACTG collaboration, P1022, undertaken to study the safety, tolerance, and efficacy of ART during and following pregnancy, the data suggests that current recommended NVP dosing for non-pregnant adults is also appropriate for pregnant women.

Observational studies of HIV-1-infected women treated with ART during pregnancy and followed for the postpartum period for evaluation are ongoing.

A5119: This drug–drug interaction study among hormone replacement therapies used by postmenopausal HIV-infected women was halted in development after findings were revealed indicating the detrimental effects of hormone replacement therapy in peri- and postmenopausal women.

Gender and Pharmacology Working Group

DACS 215: Report on the effects of sex on the PK and pharmacodynamics of NFV, IDV, and EFV and other ARV agents, combined from several AACTG studies with intensive PK measurements, is available. This analysis demonstrates a relationship between sex and PK parameters and that the relationship differs among studied ARV agents. A manuscript is in preparation.

Secondary analysis of ACTG 359 performed by this working group shows that females had a higher AUC and CMIN levels of saquinavir, as compared to males, which may attribute to the greater proportion of females having HIV-1 RNA levels ≤500 copies/mL than the males subjects.

Complications of HIV Disease RAC

A5029: This protocol examines the effect of ART on persistence of genital HPV in HIV-1-co-infected women. Preliminary data was presented at the XI International AIDS Conference in Bangkok, 2004 indicated that cervical HPV infection is common in HIV-1-infected women initiating ART.

A5163: This study aims to evaluate the effect of alendronate on HIV-1-infected subjects with decreased bone mineral density receiving calcium and vitamin D. Efforts to enroll equal numbers of male and female subjects have been hampered by the fact that fewer HIV-1-infected women screened met the criteria for enrollment.

Additional studies and analysis are underway or planned to address or examine the sex/gender effects of drugs in dysglycemic syndromes, metabolic complications, and body fat distribution abnormalities.

In the international setting, studies are being developed to assess effect and durability of ART on genital tract virus in both men and women in diverse regions of the world.

In 2002, the WHC and the Executive Committee solicited proposals for innovative interventions to enhance the recruitment of women into AACTG trials. Four sites were selected for funding and presented their findings during the summer 2004 AACTG meeting at the Recruitment and Retention of Women Symposium.

The NIAID and the National Heart, Lung, and Blood Institute sponsored a workshop in May 2003 regarding cardiovascular manifestation of HIV. WIHS, along with MACS and TAAC, have implemented an intensive protocol to evaluate cardiovascular manifestation of HIV so that gender comparisons can be made.

Highly active antiretroviral therapy has also resulted in significant declines in AIDS and death in the Women's Interagency HIV Study. WIHS compared the rates of AIDS

and/or death prior to (October 1994–April 1996) and after (April, 1996–March 1999) the time HAART became available in the United States. Despite the lack of universal use, there were substantial drops in AIDS and death from the pre-HAART to the post-HAART periods. WIHS has completed an expansion which will enable the study to evaluate clinical outcomes in the era of HAART, such as time to AIDS; impact of other infections, such as HCV; therapy use and treatment effects in women; the impact of aging on HIV disease; and the impact of hormonal factors on HIV disease.

PREVENTION

The HIV Prevention Trials Network (HPTN) is a worldwide collaborative clinical trials network designed to evaluate the safety and efficacy of non-vaccine prevention interventions, alone or in combination, using HIV incidence as the primary endpoint. HPTN research encompasses a number of important areas of women's health, including drugs and/or vaccines that are practical and easy to use to prevent mother-to-infant HIV transmission; microbicides, substances designed for vaginal or rectal use, to prevent sexual transmission of the virus; interventions to reduce behavior that exposes people to HIV; programs to check the spread of HIV through reducing intravenous drug abuse; measures to control other sexually transmitted diseases (STIs) and thereby decrease the risk of co-infection with HIV; antiretroviral therapy that may protect high-risk uninfected adults before they are exposed to HIV; and emergency therapy to treat victims of sexual assault.

The following is a list of programmatic accomplishment and developments:

- Enrollment has started during the last year for several HPTN studies (in the countries listed):
  - *HPTN 039:* Randomized phase III trial of acyclovir for reduction of HIV acquisition among high-risk individuals infected with HSV-2 (Peru, South Africa, Zambia, Zimbabwe, and the United States).
  - *HPTN 055:* A preparedness study to assess the ability of sites to recruit and retain participants for future efficacy trials of topical microbicides, and to develop reliable data on HIV seroprevalence and seroincidence in the target populations (South Africa, Tanzania, and Zambia).
- Enrollment continued during the past year for these previously activated trials (in the countries listed):
  - *HPTN 034:* A preparedness study to determine local infection rates and to assess site capacity for enrollment and retention (India).
  - *HPTN 040:* A randomized comparative trial of three antiretroviral regimens for post-exposure prophylaxis of HIV-uninfected infants born to HIV-infected women whose HIV status was unknown at the time of delivery and who, therefore, were not exposed to a prenatal or perinatal antiretroviral regimen.
- Enrollment has been completed for these studies (in the countries listed), which are continuing with participant followup and/or data analysis:
  - *HIVNET/HPTN 024:* A phase III trial of antibiotics to reduce chorioamnionitis-associated perinatal transmission of HIV (Malawi, Tanzania, and Zambia). Enrollment into this trial was terminated when it was determined that no statistically significant conclusion could be reached. Followup continues for children born to mothers enrolled into this trial.
  - *HPTN 033:* A preparedness study to determine local infection rates and to assess site capacities for enrollment and retention (China, India, and Russia). These sites are continuing followup of enrolled participants.

- These network clinical trials have been completed in the past year (in the countries listed):
  - *HIVNET 012:* A phase IIb trial to determine the efficacy of oral AZT and the efficacy of oral nevirapine for prevention of perinatal transmission of HIV (Uganda)
  - *HPTN 047:* A phase I study of the vaginal microbicide PRO 2000/5 gel (P) (India). Preliminary analysis of the study results show that 0.5 percent PRO200/5 Gel (P) was acceptable to the women and their partners, without the identification of any significant safety concerns.
  - *HPTN 049:* A phase I study of the vaginal microbicide cellulose sulfate in HIV-infected women (United States). Preliminary data analysis has revealed that CS gel was well tolerated with no severe or life-threatening averse events.
  - *HPTN 050:* A phase I study of the vaginal microbicide PMPA gel (United States). Preliminary analysis of the trial data has revealed no significant safety concerns for PMPA gel. PMPA gel was generally acceptable to the women and their participating partners.
- Integration of prevention research and treatment research through coordination of HPTN and AIDS Clinical Trials Group (ACTG) studies. The studies, HPTN 052 and ACTG 5175, are finalized and will be conducted at previously established HPTN sites in India, Thailand, Brazil, Malawi, Zimbabwe, and the United States. Both networks are coordinating their approach to site preparation, training, data acquisition, and data storage to facilitate the participation of site staff with both studies. The studies are:
  - *HPTN 052:* Randomized trial of intensified primary care for HIV infection versus intensified primary care plus highly active antiretroviral therapy administered to the HIV-infected index partner in HIV-serodiscordant couples, as a means of reducing sexual transmission of HIV (Brazil, India, Malawi, Thailand, and Zimbabwe). The trial is designed to determine if reducing viral load can also reduce the risk of sexual transmission of HIV.
  - *The therapeutics trial that will be linked to HPTN 052 is ACTG 5175:* It will enroll HIV-infected participants who are ineligible for HPTN 052 due to low CD4 counts or to the presence of AIDS-defining illness. A5175 will examine the comparative efficacy of different antiretroviral drug regimens that are expected to be available in developing county settings.
- *Other studies of MTCT:* Enrollment is underway for a three-site, investigator-initiated study supported by cooperative agreement awards. This study is a randomized efficacy trial in Ethiopia (PI: Andrea Ruff), India (PI: Robert Bollinger), and Uganda (PI: Brooks Jackson) to evaluate a 6-week regimen of nevirapine administered to HIV-uninfected infants born to HIV-infected breastfeeding mothers. The Uganda site is alsorandomizing to an open-label arm that passively immunizes breastfeeding children with HIV-immune globulin (HIV-Ig). All sites are actively enrolling.

Perinatal Transmission

Studies for the prevention of perinatal transmission are conducted through the Pediatric AIDS Clinical Trials Group and the HIV Prevention Trials Network.

In the Pediatric AIDS Clinical Trials Group, a number of early, Phase I studies are closed and in various stages of data analysis. These include:

- *PACTG 386:* A Phase I trial of the safety, pharmacokinetics, and tolerance of fortovase (saquinavir SGC) co-administered with low dose zidovudine (ZDV) and lamivudine (3TC) in HIV-infected pregnant women during gestation and postpartum, and in their infants' post-maternal dosing. (Prepared and submitted final study data to pharmaceutical company.)

- *PACTG 358:* A Phase I trial of the pharmacokinetics, safety, and tolerance of indinavir when given in combination with 3TC and ZDV to HIV-infected pregnant women. The study will also assess the pharmacokinetics of indinavir in cord blood and neonatal samples following maternal dosing, and the safety and tolerance of prior maternal dosing in the newborn. (Prepared and submitted final study data to pharmaceutical company.)

- *PACTG 354:* A Phase I study of the safety, tolerance, and pharmacokinetics of ritonavir when given in combination with 3TC and ZDV to HIV-infected pregnant women. The study will assess the pharmacokinetics of ritonavir in cord blood and neonatal samples following maternal dosing, and the safety and tolerance of prior maternal dosing in the newborn. It will also determine an initial dosage regimen of ritonavir for infants up to 4 weeks of age.

- *PACTG 353:* A Phase I study to assess the pharmacokinetics of nelfinavir when given in combination with ZDV and 3TC, and to assess the safety and tolerance of the triple-combination therapy in HIV-infected women during pregnancy and postpartum, and in HIV-exposed infants. (Collaborated on infant manuscript development. The manuscript is completed and ready for PACTG review. Collaborated on maternal manuscript development.)

- *PACTG 316:* A followup of an earlier study conducted in Uganda that reported a marked reduction in mother-to-child transmission of HIV with a single dose of nevirapine to mother and infant regimen. In order to determine if this same simple regimen could further reduce the rates of HIV transmission in the United States, Europe, Brazil, and the Bahamas, PACTG 316 included 1,270 women who received their country's standard of care for their health status. Most of these women received combination antiretroviral therapy during pregnancy, and about a third of the women had elective cesarean delivery. The study was stopped early, at the recommendation of NIAID's Data and Safety Monitoring Board (DSMB), because the overall mother-to-infant transmission rate was 1.5 percent, a much lower rate than originally anticipated and one which made it impossible to assess an additional beneficial effect of nevirapine with the planned study design. The nevirapine two-dose regimen was well tolerated by both mothers and infants; no differences were seen in toxicity assessments between the placebo and nevirapine arms. This study demonstrates the dramatic reductions in mother-to-child transmission of HIV that can be achieved when HIV-infected women receive current obstetrical and antiretroviral standard of care as recommended by the Public Health Service perinatal treatment guidelines. Completed analyses to explore factors that contribute to the observed differences in risk of HIV transmission between whites and non-whites enrolled in PACTG sites in the United States. Manuscript has been published. NVP pharmacology analysis manuscript completed and published. Analyses on infant toxicity outcomes according to maternal antiretroviral therapy during pregnancy are in final phases of medical review. Analyses to explore the use of interventions to reduce HIV vertical transmission and differences between Europe and the United States, in terms of use of interventions, are being completed and a manuscript is in preparation.

- NIAID-funded researchers recently examined the emergence and fading of nevirapine (NVP) resistance (NVP(R)) mutations in HIV-1-infected Ugandan women and infants who received single-dose NVP to prevent HIV-1 mother-to-child (vertical) transmission. NVP(R) was examined in women and infants who received a single dose of NVP in the HIVNET 012 clinical trial. In summary, NVP(R) was detected more frequently in infants than women following NVP prophylaxis, and different patterns of NVP(R) mutations were detected in women versus infants. NVP(R) was detected infrequently in infants with late HIV-1 infection. NVP-resistant HIV-1 faded from detection in both women and infants over time.

- In the HIV Prevention Trials Network (HPTN), a Phase III trial of antibiotics to reduce chorioamnionitis-associated perinatal transmission of HIV (HIVNET/HPTN 024) was initiated in Malawi, Tanzania, and Zambia.

- Enrollment is underway for two investigator-initiated studies supported by cooperative agreement awards. These studies—one in Ethiopia and one in India—are designed to evaluate a 6-week regimen of nevirapine administered to HIV-uninfected infants born to HIV-infected breastfeeding mothers. A third similar trial is expected to begin enrollment in 2003 in Uganda, and will include an additional arm that examines the benefit of administering HIV-immune globulin (HIVIg) to the infant.

- A small retrospective study had previously raised concerns that HIV-infected pregnant women, who received combination antiretrovirals for their health and to reduce the risk of HIV transmission to their infants, had an increased risk of premature delivery. As a result, researchers compiled data from seven clinical studies of HIV-infected pregnant women (including the Women and Infants Transmission Study and Pediatric AIDS Clinical Trials Group protocols) to better assess the risk of adverse outcomes of pregnancy. Overall, combination antiretroviral therapy was not associated with a risk of an adverse outcome, such as premature delivery or low birth weights. The use of potent combination antiretroviral regimens is recommended by Guidelines issued by the Public Health Service for most HIV-infected pregnant women, and is associated with a dramatic decrease in the rate of mother-to-child HIV infections. This study provides information on the safety of these regimens that is likely to be reassuring to HIV-infected pregnant women and their health care providers.

Vaccines

Vaccines can provide a safe, effective, and efficient means to prevent illness, disability, and death from infectious diseases. Research leading to new and improved vaccines is a high NIAID priority. In addition to improving the health of the public, vaccines have been shown to greatly reduce both direct and indirect health care costs. Recent accomplishments include the establishment of two new comprehensive research networks, one focused on HIV vaccines and one on prevention research. The HVTN has completed several studies and is currently reviewing the data.

- *HVTN 039*: A study to evaluate the safety and tolerability of two-dose levels of a potential HIV prevention vaccine called vCP1452, which is a live recombinant Canarypox vaccine. Two HIV genes are inserted into the canarypox vector to make the vaccine. Canarypox virus is a live virus that is not disease producing and is used only to carry the two HIV genes into the body. Once the genes are in the body, it is hoped that the body will make antibodies against the HIV genes.

- *HVTN 041*: A Phase I vaccine study to test the safety and tolerability of a combination preventive HIV vaccine in men and women. The vaccine is made of a combination of the NefTat vaccine and the gp120 vaccine with adjuvant ASO2A. The NefTat vaccine is formed from a protein made by yeast cells. This is the first time the NefTat vaccine has been tested in humans.

- *HVTN 203*: A Phase II study of two experimental HIV vaccines tested the safety of the vaccines, studied how the immune system responds to them, and tested different ways of combining these two vaccines. The study tested AIDSVAX B/B, made from synthetic gp 120, a protein that forms part of the outside coating on the HIV virus. AIDSVAX B/B is designed to help the body make antibodies that might prevent HIV from infecting cells. The other vaccine tested is ALVAC-HIV (vCP1452), made from a canarypox virus that contains man-made copies of a few HIV genes. This vaccine is made to help the body make cytotoxic T lymphocytes (CTLs), which might kill HIV-infected cells.

- *HIVNET 026*: The purpose of this study is to test how the body's immune system responds to the vaccine ALVAC-HIV

vCP1452 and to determine if the vaccine is safe when given alone and with MN rgp120 in populations outside the United States.

- The following protocols have been completed: HVTN 039, 041, 203, and 026.
- The following protocols are no longer recruiting: HVTN 040, 042, 044, and 048.

Other Sexually Transmitted Infections

The number of cases of sexually transmitted diseases (STIs) continues to increase dramatically worldwide, yielding serious economic, social, and health consequences. According to the Centers for Disease Control and Prevention (CDC), more than 65 million people live with an incurable STI in the United States, with an additional 15 million people acquiring one or more STIs each year, some of which have lifelong consequences. STIs are critical global and national health priorities because of their devastating impact on women and infants, and interrelationships with HIV/AIDS. STIs can lead to infertility, tubal pregnancy, cervical cancer, low birth weight, congenital/perinatal infections, increased risk of HIV infection, and other chronic conditions such as neurosyphilis.

The NIAID supports a broad STI research portfolio (*http://www.niaid.nih.gov/dmid/stds/*) addressing these diseases through investigator-initiated research grants and a variety of research programs, including the: 1) STI Cooperative Research Centers (CRCs), which bridge basic biomedical, clinical, behavioral, and epidemiological research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research; and 2) STD Clinical Trials Unit, which conducts clinical trials to test safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STIs.

PREVENTION AND RISK FACTORS

- Several promising vaccine candidates for the prevention of gonorrhea have been identified.
- Protegrins, a novel class of microbicides that are active both *in vivo* and *in vitro*, have a broad antimicrobial spectrum that includes, *Haemophilis ducreyii*, *Chlamydia trachomatis*, *Candida albicans*, and HIV-1.
- Clinical studies on a lactobacillus suppository to prevent bacterial vaginosis were initiated in August 2000.
- Two studies on adolescents and social/sexual networks were started in FY 2000. The emphasis is on adolescent development and the acquisition of infection, including risk factors, immunologic correlates of viral STD pathogens, and the diffusion of infection through networks of sexual partners.
- NIAID researchers continued their efforts to develop a chlamydia vaccine. Earlier approaches using various pieces of the organism were unsuccessful, so the scientists are now developing candidate vaccines using live, weakened chlamydia strains.
- NIAID scientists compared the prophylactic and therapeutic usefulness of three different classes of candidate HSV-2 vaccines given in four regimens to two species of animals. One of these, called dl5-29, appears to be a good candidate for early-phase human trials.
- The NIAID completed participation in a multicenter study to evaluate an antiviral drug, valacyclovir, for preventing the transmission of herpes simplex virus (HSV) in heterosexual couples in which only one member was infected with HSV. Approximately 1,500 couples took part in the study at outpatient centers in the United States, Canada, and Europe. The study found that the risk of acquiring a clinical genital herpes infection among susceptible persons taking the drug was 77 percent lower than among those receiving a placebo. This finding and additional study data have encouraged the maker of valacyclovir to pursue FDA approval.
- The STD Prevention Primate Unit for preclinical evaluation of topical microbicides (TM) and vaccines at the University of Washington has evaluated several candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques this past year. These evaluations assist in informing product development and the

design of safety and efficacy testing in clinical trials.

- The Herpevac Trial for Women is a pivotal Phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. The trial is enrolling 7,550 women at approximately 35 sites. This study is being conducted as a public–private partnership with GlaxoSmithKline (*http://www.niaid.nih.gov/dmid/stds/herpevac/about_herpes.htm*).

- **Sexually Transmitted Infections and Topical Microbicides Cooperative Research Centers (STI TM CRCs)** This Request for Applications was released August 25, 2003. This FY 04 initiative was a recompetition of the Sexually Transmitted Diseases Cooperative Research Centers (RFA-NIH-AI-98-007) that refocused and expanded the CRCs in order to develop better approaches for the diagnosis, prevention, and treatment of STIs. Six CRCs have been awarded. (RFA-AI-03-042)

- The Sexually Transmitted Disease Clinical Trials Unit has completed a multisite clinical study to determine the concordance of trichomoniasis between male and female partners. Data from this study will assist in the design of domestic clinical trials to evaluate topical microbicides.

- A NIAID-supported randomized controlled clinical trial demonstrated that once-daily valacyclovir reduces the risk of transmission of genital herpes to uninfected partner.

- A NIAID-supported study showed that leading-candidate topical microbicides inhibit *Neisseria gonorrhoeae* genital tract infection in a mouse model.

Treatment

- A study is underway to evaluate the efficacy of azithromycin as antibiotic therapy for early syphilis compared to the current recommended treatment: benzathine penicillin G. The current treatment is administered as an intramuscular injection, whereas azithromycin, as an oral dose, would be much easier to administer and would be offered as an alternative for patients who are allergic to penicillin.

- Research is progressing on the development of natural and synthetic porphyrins and metalloporphyrins (MPs). These compounds possess potent and broad-spectrum antibacterial activity. A number of porphyrin compounds have been found to have potent virucidal activity against HSV-2 alone, and against both HSV-1 and HSV-2.

- NIAID scientists identified a chlamydial protein that promotes entry into the host cell where it can cause infection and disease. This protein is a potential new target for anti-chlamydia drug development.

Diagnostics and Screening

- The NIAID continues to provide support for the development and evaluation of STD diagnostics through the Small Business Innovation Research (SBIR) mechanism.

- NIAID researchers performed several studies comparing self-administered vaginal swabs, cervical swabs, and first-catch urines for the diagnosis of chlamydial infections in women. Specimens from 22,517 15- to 25-year-old asymptomatic women attending clinics in nine different centers in the United States were evaluated. Overall, chlamydia prevalence was 13 percent. Results with a self-administered versus a clinician-collected vaginal swab were equivalent and were at least as good as results with first-catch urines and cervical swabs. These studies demonstrate that vaginal swabs are appropriate specimens for diagnosing chlamydial genital tract infection by amplified diagnostic assays.

Animal Models

- Research is progressing on the development of a human vaginal graft model in immunocompromised mice.

- Research is progressing on the development of a mouse animal model of gonococcal infection.

- NIAID scientists are using a mouse model of chlamydia genital infection to test candidate chlamydia vaccines.

- Research is progressing on the development of a new nonhuman primate model of HIV infection with multiple low-dose viral exposures to more closely mimic human transmission.

GENOMICS

- In FY 2000, the NIAID's genomic sequences of *Neisseria gonorrhea*, *Haemophilis ducreyi*, *Chlamydia trachomatis*, and *Treponema palladium* were completed. The genome sequence of *Lactobacillus crispatus* (normal vaginal flora) and *Ureaplasma urealyticum* were also initiated. These genome sequences have provided new insights into the pathogenesis of these diseases, and pave the way for new diagnostic, drug, vaccine, and microbicide development opportunities.

- In FY 1999, the NIAID established a relational database (STD GEN) for pathogens that cause sexually transmitted diseases (*http://www.stdgen.lanl.gov*), at the Los Alamos National Labs, to serve as an international resource for the compilation, analysis, and dissemination of genetic sequence and associated data for STD pathogens. In FY 2000, several new features were added, and the genomic sequence of type-1 HSV was incorporated.

- The NIAID supported sequencing of the *Trichomonas vaginalis* genome. *T. vaginalis* causes the sexually transmitted infection trichomoniasis, which is one of the most common non-viral genital tract infections worldwide. Trichomoniasis is associated with pre-term and low birthweight deliveries and increases susceptibility to, and transmission of, HIV infection in women. Documentation of the Trichomonas genome project and resulting sequence data is available at *http://www.tigr.org/tdb/e2k1/tvg/*.

More information on advances related to STDs may be found in the Topical Microbicide and Vaccine sections.

Topical Microbicides

HIV/AIDS and other STIs are spread predominantly through sexual transmission. Therefore, the development of chemical and biologic barriers that can be used intravaginally or intrarectally, with or without physical barriers, to inactivate HIV and other STIs is critically important for controlling infection. Across the globe, women face the greatest risk of acquiring HIV and STIs due to substantial mucosal exposure to seminal fluids; the prevalence of non-consensual sex; sex without condom use; and hidden, high-risk behaviors of their partners. Despite the overwhelming risks presented to them, women have the fewest available means for protection against HIV and other STIs. An inexpensive, reliable, female-initiated method for preventing STIs is urgently needed so that women can protect themselves. Ideally, chemical or biologic barriers, known as topical microbicides, should be unobtrusive, non-irritating, safe, acceptable, and inexpensive. In addition, microbicides should be available in both contraceptive and non-contraceptive formulations since women presently may put themselves at risk for acquiring HIV and other STIs in order to conceive a child.

The NIAID's research effort for the development of topical microbicides includes basic research, preclinical product development, and clinical evaluation. A number of animal models currently exist for testing microbicides, including nude mice for HPV infection, macaques for simian immunodeficiency virus (SIV), and dimian/human immunodeficiency virus (a modification of SIV that contains key elements of HIV) infection, and guinea pigs and mice for genital herpes.

Research continues to evaluate and confirm the use of animal models for evaluating topical microbicides. NIAID-funded researchers have established a reproducible non-human primate model for studying safety and effectiveness of a topical microbicide for the prevention of chlamydial infection. This research found that the anatomy and vaginal flora of pigtail macaque monkeys and humans are remarkably similar.

Several significant research advances include:

- **A Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel**
  This clinical trial was completed at three domestic sites within the HIV Prevention Trials Network (HPTN). The objectives of the study were to determine: 1) the safety and acceptability of PMPA gel for vaginal use among sexually abstinent and active HIV-uninfected and -infected women, and 2) the acceptability of PMPA gel among their male sexual partners (when relevant). The full protocol is available at *http://www.hptn.org*. Preliminary analysis of the trial data has revealed no significant safety concerns for PMPA gel; most adverse events were mild. PMPA gel was generally acceptable to the women and their partners who participated in the study. (HPTN 050)

- **Phase I Safety and Acceptability Study of the Vaginal Microbicide 6 Percent Cellulose Sulfate Gel among HIV-infected Women**
  This clinical trial was completed at four domestic sites within the HPTN. The purpose of the study was: 1) to assess the safety and acceptability of 6 percent cellulose sulfate (CS) gel for vaginal use versus a control gel among HIV-infected women, and 2) to assess the acceptability of CS gel among the HIV-infected male sexual partners of female participants. The full protocol is available at *http://www.hptn.org*. Preliminary analysis of the data has revealed that CS gel was well tolerated with no severe or life-threatening adverse events. (HPTN 049)

Several studies of topical microbicides have been initiated, including:

- **A Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5 Percent PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women**
  This is a four-arm, multisite, randomized controlled trial comparing BufferGel and 0.5 percent PRO 2000/5 Gel (P) with a placebo gel and with no treatment. The three study gel arms will be double blinded. The Phase II expanded safety portion of the study will be conducted as an uninterrupted lead-in to the Phase IIb preliminary effectiveness portion, including approximately 3,220 sexually active HIV-uninfected women from sites in Blantyre, Malawi; Chililabombwe and Lusaka, Zambia; Chitungwiza and Harare, Zimbabwe; Durban and Hlabisa, South Africa; Lilongwe, Malawi; Moshi, Tanzania; and Philadelphia, Pennsylvania. (HPTN 035)

Other studies that have either been completed or are still underway include:

- A multisite clinical study to determine the concordance of trichomoniasis between male and female partners being conducted by the DMID Sexually Transmitted Disease (STI) Clinical Trials Unit. This will include a microbicide acceptability questionnaire. Data from this study will provide STI prevalence that will be relevant for future domestic microbicide efficacy trials.

- **HIV Prevention Preparedness Study**
  This study was initiated and continues to accumulate patients at four international sites in Zambia, South Africa, and Tanzania in preparation for implementation of HPTN 035. The purpose of this study is to assess the ability of sites to recruit and retain participants for future efficacy trials of topical microbicides, including HPTN 035, and to develop reliable data on HIV seroprevalence and seroincidence in the target populations. The full protocol is available at *http://www.hptn.org*. One site in Durban, South Africa has completed the study and was the first site to enroll participants in HPTN 035. (HPTN 055)

A number of programmatic accomplishments have also been made to help further topical microbicide research.

- The NIAID Microbicide Strategic Plan, a document that provides a detailed long-range plan for advancing microbicide concepts from the laboratory to clinical trial evaluation, was officially released at the Microbicides 2004 Conference in London, UK, and was placed on the NIAID HIV Prevention website (*http://www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf*) and released in pamphlet form in March 2004.

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM)** Awards were made to three multidisciplinary, multi-project programs submitted in response to a Program Announcement (PA) co-sponsored with the NICHD. The purpose of the PA is to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goals are to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations, and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segued into the studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network. New awards funded by NIAID were made to:

  - Dr. Tom McCarthy, StarPharma Ltd., **Development of Dendrimer and Combination Microbicides**, 1-U19-AI-60598

  - Dr. Peter Anton, UCLA, **The Microbicide Development Program**, 1-U19-AI-60614

  - Dr. John Lewicki, Osel Inc., **Lactobacilli as a Delivery Vehicle for Microbicides**, 1-U19-AI-60615

These three new awards significantly expand the scope of the IPCP-HTM introducing programs focusing on development of combination inhibitors using dendrimer platform technology, rectal microbicide development, and delivery strategies using engineered Lactobacilli. (PA-03-137)

- **Sexually Transmitted Infections and Topical Microbicides Cooperative Research Centers (STI TM CRCs)** The Request for Applications was released August 25, 2003. This FY 2004 initiative was a recompetition of the Sexually Transmitted Diseases Cooperative Research Centers (RFA-NIH-AI-98-007) that re-focused and expanded the CRCs in order to develop better approaches for the diagnosis, prevention, and treatment of STIs. (RFA-AI-03-042)

Six CRCs have been awarded to:

- Dr. Charles J. Arntzen, Arizona Biodesign Institute, Arizona State University, **Plant-made Microbicides and Mucosal Vaccines for STIs**, 1-U19-AI-62150-01

- Dr. Joel B. Baseman, University of Texas Health Sciences Center at San Antonio, **San Antonio STI TM CRC**, 2-U19-AI-45429-06

- Dr. King K. Holmes, Center for AIDS and STD Harborview Medical Center, **University of Washington STI TM CRC**, 2-U19-AI-31448-14

- Dr. David Martin, Louisiana State University, **Gulf South STI TM CRC**, 1-U19-AI6-1972-01

- Dr. P. Frederick Sparling, The University of North Carolina–Chapel Hill, **North Carolina STI TM CRC**, 2-U19-AI3-1496-14.

- Dr. Stanley M. Spinola, Indiana University, **Midwest STI TM CRC**, 2-U19-AI-31494-14

- **Specialized *in Vitro* Virological Evaluations of Strategies to Combat HIV/AIDS** Principal Investigator: Dr. Brigitte Beer. In the past year, 345 (71 active) NCI compounds and 28 (20 active) NIAID compounds were tested under the contract. A total of 1,442 assays were performed: 36 ME180 assays, 901 CD4-dependent assays (164 repeats), 83 CD4-dependent plus mucin assays (seven repeats), 226 attachment/fusion assays (23 repeats), and 48 lactobacillus assays (one repeat). The 33 most promising NCI compounds are undergoing evaluation as topical microbicide candidates. (N01-AI-05415)

  - ***pH transition assay***
    Since the vaginal pH of sexually mature women is approximately 4, and the normal ejaculate of men is a basic pH (i.e., 7.2 to 7.8), topical microbicide candidates must be active over a wide pH range. Previously, a pH transition assay was developed for X4-tropic

HIV to mimic the events a compound would encounter during sexual intercourse. During the past year, a new pH transition assay was developed specific for R5-tropic HIV-1. A total of 95 R5-specific and 6 X4-specific pH transition assays were performed.

- ***Seminal plasma assay***
  An assay was developed to determine whether seminal plasma inhibits topical microbicide candidates known to be active in the R5-tropic cell-to-cell HIV transmission inhibition assay. A commercial supply of seminal plasma was identified and the plasma from five donors pooled to minimize donor-to-donor variation. The first round of testing is in progress.

- The STD Prevention Primate Unit for preclinical evaluation of topical microbicides and vaccines at the University of Washington has continued to evaluate candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pigtailed macaques this past year. Please note the *Scientific Advance* publication summary (above), Use of a Rhesus Macaque Model to Evaluate Vaginal and Rectal Safety of Candidate Microbicides. Results from the DMID-supported testing contract are being coordinated with testing being conducted by DAIDS to facilitate product development and safety and efficacy testing in clinical trials. (DMID contract N01-AI-95388)

- The Sexually Transmitted Infections Clinical Trials Group was successfully recompeted. The contract will support clinical studies to evaluate control and prevention strategies, such as topical microbicides for STIs. Two awards were made in FY 2004.

- **HIV Microbicide Design and Development Teams**
  This Request for Proposal is a newly established milestone-driven program released with an anticipated FY 2005 award date. The contracts will support streamlined development of microbicide candidates, emphasizing combination products with multiple active agents. Initiation of a Phase I safety trial is required within the award period.

- A Master Contract for Preclinical Development was awarded to Advanced Bioscience Laboratories, Inc., in August 2004. The contract will help the NIAID staff identify potential new microbicide candidates and provide all support needed for small-scale production and packaging, preclinical testing, and documentation leading to IND submission for Phase I clinical testing.

- An External Scientific Review Panel of outside experts was convened on May 15, 2003, in Bethesda, MD, to review a proposed trial, designated HPTN 035, to be conducted within the HIV Prevention Trials Network (HPTN). HPTN 035 is a Phase II/Ilb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5 Percent PR02000/5 Gel (P) for the Prevention of HIV Infection in Women. The overall charge to the panel was to advise whether:

  - the study products were appropriate for testing in an advanced clinical trial; and

  - the scientific/statistical design of the protocol was sound and feasible for the planned study sites.

  The panel's recommendations confirmed the merit of the trial proposed in the context of the current status of the microbicide pipeline and underscored the likelihood of achieving the proposed objectives at the selected study sites.

- The Topical Microbicides Development and Evaluation Workshop was the first joint meeting of the DMID-, DAIDS-, and NICHD-supported investigators with Topical Microbicide P01s and U I9s. The workshop, held March 18-20, 2003, focused on issues ranging from basic research through formulation and applicator design, and served as a forum for establishing collaborations among STI and HIV investigators in the microbicide arena.

NIAID scientists have continued to make important discoveries that promote the development of an effective, easy-to-use, female-initiated method to protect from sexual transmission of HIV. Based on their fundamental insights into how HIV gains entry into target cells, NIAID scientists designed a novel agent to neutralize HIV infection, which they plan to develop as a topical microbicide for preventing sexual transmission of HIV. Research is ongoing to make the inhibitor effective against a wide array of HIV strains. Progress has also been made in engineering lactobacillus, a bacterium normally found in the vagina, to produce this inhibitor. Researchers believe that colonizing the vaginal tract with the engineered lactobacillus may provide a method for durable protection against sexual transmission of HIV that is economically feasible and controlled by women.

HIV can be broadly divided into X4 and R5 viruses by its preference (tropism) for infection of T cells and monocyte/macrophages, respectively. The designations X4 and R5 are shorthand abbreviations for the chemokine receptors CXCR4 (X4) and CCR5 (R5), the primary cellular receptors (co-receptors) needed, in addition to CD4, for entry of HIV into cells. Although the ejaculate may contain both X4 and R5 viruses, R5 viruses are selectively transmitted. Thus, it has been hypothesized that an effective microbicide strategy will be one that will block the interaction of the virus with the R5 co-receptors. PSC-RANTES is an optimized derivative of the natural R5 receptor ligand RANTES, and has been demonstrated by this group and others to be able to block transmission and infection of R5 virus in tissue culture assays. NIAID-supported investigators presented the first evidence that an anti-R5 strategy will work to prevent transmission of virus *in vivo*. Prior to intravaginal challenge with SHIV162P, PSC-RANTES was administered topically to macaques that were made more susceptible to HIV infection by pre-treatment with progestin. At the highest does of PSC-RANTES, all macaques (three of three) were protected from infection. At lower doses, only some of the animals were protected. For those that became infected, the overall magnitude of infection was decreased (total viral RNA copies), with a corresponding increase (delay) in the time to peak infection. All of the macaques in the control group were pre-treated with buffer and became infected (ten of ten). These studies provide the first solid evidence that strategies aimed at preventing transmission of virus by targeting its preferred co-receptor can be effective. This study represents a major proof of concept for the development of R5 HIV co-receptor inhibitors as microbicides.

Tuberculosis

Tuberculosis (TB) is an ancient bacterial infection caused by *Mycobacterium tuberculosis*. The bacteria are spread from person to person by airborne droplets expelled from the lungs when a person with active TB disease coughs, sneezes, or speaks. Infection typically takes root in the lung air sacs. In healthy people, TB infection is barricaded behind a "wall" of cells that limits the spread of TB within the host. This contained infection is referred to as latent or persistent TB and may be present throughout an individual's lifetime. If the body's immune system becomes weakened from HIV infection, malnutrition, aging, or other factors, the bacteria may become "re-activated" and begin to spread within the lungs or to other tissues resulting in active and infectious TB.

In most of the world, more men than women are diagnosed with TB and die from it (WHO). However, TB is the leading infectious killer of women of reproductive age worldwide, causing more deaths in women than all causes of maternal mortality combined (WHO report on the Tuberculosis Epidemic, 1996). Across the world, more than 900 million women between ages 15 and 44 are infected with TB; 2.5 million get sick and 1 million die from TB each year (WHO press release, 1998). DMID supports a robust portfolio of basic and applied TB research projects (*http://www.niaid.nih.gov/dmid/tuberculosis/*).

DMID is not currently conducting any studies that target tuberculosis in women specifically. However, DMID supports a wide range of tuberculosis research, including diagnostic, vaccine and therapeutic discovery, development, and clinical testing that have the potential to benefit women, children, and men at risk for or affected by TB.

Immunology and Immune-mediated Diseases

Autoimmune Diseases

The immune system normally makes antibodies that attack invading pathogens in an effort to protect the body from infection and injury. In the case of autoimmune diseases, however, the immune system makes autoantibodies, or antibodies against self, that attack the body's own tissues. Physicians and scientists have identified more than 80 distinct autoimmune diseases that affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. These diseases are a significant cause of chronic morbidity, costing billions of dollars annually in health care expenses and lost productivity. The NIAID has placed a high priority on research in autoimmunity and autoimmune diseases, and supports a broad portfolio of basic, pre-clinical, and clinical research aimed at understanding the pathogenesis of these chronic diseases, investigating new ways to modify the immune response, and applying this knowledge to the identification and evaluation of promising approaches to treat and prevent these diseases. Research on the immune system in the last two decades has resulted in a wealth of new information and extraordinary growth in understanding the immune system. These accomplishments now provide promising opportunities for major advances in the diagnosis, treatment, and prevention of autoimmune diseases.

Scientific Advances

Gender-specific T Cell Homing and Autoimmunity
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.

Sex-based Differences in the Immune Response
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.

Sex Hormone Regulation of Innate Immunity
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 hormones and pathogen 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.

Risk

The NIAID joined the NIAMS, the NCI, and the ORWH, in supporting an IOM study to evaluate the status of research related to the safety of silicone gel breast implants. One aspect of the study evaluated research regarding the immune response to silicone. According to the report, post-operative infections/complications pose the major health risk

associated with silicone gel breast implants. This risk is compounded by the fact that follow-up procedures, such as replacement of leaking implants, are often required. The IOM found no reliable data to support the claim that silicone breast implants increase a woman's risk for developing autoimmunity, and that many of the studies published to date on the impact of silicone gel breast implants are seriously flawed. Results, published June 1999, and can be obtained online at *http://www.nap.edu/books/0309065321/html*.

TREATMENT

- An important study conducted by the Autoimmunity Centers of Excellence demonstrated that the loss of insulin production in patients with new-onset type-1 diabetes can be diminished for 1 year after treatment with a recombinant anti-T monoclonal antibody. Further trials will be needed to determine the longer-term benefits of this experimental therapy. Nonetheless, these preliminary results indicate that novel immune therapies can interrupt the destructive immune processes in autoimmune diseases and have potentially long-lasting effects. A larger Phase II trial is in development in the Immune Tolerance Network. If successful, this treatment could dramatically improve the quality of life for those afflicted with type 1 diabetes.

Multidisciplinary Research Programs

- **Autoimmunity Centers of Excellence** The nine Autoimmunity Centers of Excellence (ACEs) conduct collaborative basic and clinical research on autoimmune diseases, including single- and multi-site pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. The ACEs support close interaction between clinicians and basic researchers, which should facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. Examples of ACEs-supported clinical trials include: anti-CD20 for systemic lupus erythematosus (SLE); sirolimus for multiple sclerosis; and a double-masked study of the combination of copaxone and albuterol versus copaxone alone for multiple sclerosis. The ACEs are co-sponsored by the NIDDK and the NIH ORWH.

- **Immune Tolerance Network (ITN)** An international consortium of over 80 investigators in the United States, Canada, Europe, and Australia dedicated to: the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, the ITN has established state-of-the-art core laboratory facilities to conduct integrated mechanistic studies, and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. These core facilities include microarray analyses of gene expression, bioinformatics approaches to develop analytic tools for clinical and scientific data sets from the ITN-sponsored trials, ELISPOT analyses of protein expression, and cellular assays for T cell reactivity. Currently, the ITN has 14 clinical trials for autoimmune diseases ongoing or in development. The ITN, co-sponsored by the NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), will be recompeted in FY 2006. More information on the ITN is available on its website at *www.immunetolerance.org*.

- **Autoimmune Disease Prevention Centers** These centers conduct research on the development of new targets and approaches to prevent autoimmune diseases and evaluates these approaches in pilot and clinical studies. In FY 2004, the prevention centers supported 16 pilot projects to test innovative approaches that may lead to the development of novel targets for disease prevention or assays for biomarkers

of disease progression. The prevention centers are co-sponsored by the NIDDK, the NICHD, the ORWH, and the JDRF.

- **Sex-based Differences in the Immune Response Research Initiative**
  The NIAID, in collaboration with the NIAMS, the NINDS, the ORWH, and the National Multiple Sclerosis Society, supports this initiative. In addition, the NIAID, with the NIH OAR and the NIH ORWH, support a program project to investigate the differences in the immune response in the female reproductive mucosa. While differences in the immune response of males and females have been documented, including the increased incidence of autoimmune diseases in women, the reasons for pregnancy-induced changes in immune-mediated diseases, and differences in the rate and severity of disease, are unclear. Increased understanding of the mechanisms underlying the differences in the immune response in males and females should allow more targeted approaches for the prevention and treatment of immune-mediated disease.

- **Stem Cell Transplantation for Autoimmune Diseases Consortium**
  The consortium is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat severe multiple sclerosis, systemic lupus erythematosus, and scleroderma. These complex trials are expected to open in 2005. The consortium will also conduct studies of the underlying immune mechanisms of these diseases.

Animal Models

- **New Mouse Model of Systemic Autoimmune Disease**
  NIAID scientists developed a new mouse model of systemic autoimmune disease. The mice are deficient in a molecule that inhibits antibody production and inflammatory responses, allowing some of them to develop a spontaneous disease that resembles lupus in humans. The scientists have discovered several genes that appear to control whether these animals develop SLE. These newly discovered genes may help scientists develop new methods to treat lupus, or other autoimmune diseases, and will serve as predictors of disease susceptibility, progression, and severity.

Research Resources

- **Multiple Autoimmune Disease Genetics Consortium (MADGC)**
  The MADGC was established by the NIAID in FY 1999. The consortium collects medical information, cells, serum, and genetic material (DNA) from families in which two or more individuals are affected by two or more distinct autoimmune diseases. In February 2004, the NIAID hosted a panel of experts in disease gene mapping to review the current status of the specimens and information collected by the MADGC. The panel commended the consortium on its efforts and recommended a detailed analysis of a subset of specimens in the repository to assess the potential value of the resource. It is anticipated that the results of this analysis will be available in early 2005. To date, 263 families have been fully enrolled and 94 families are in the process, working toward the goal of 400 families enrolled in 2004. This database and repository of associated materials will promote the discovery of human immune response genes involved in autoimmunity. For more information go to *http://www.madgc.org/*.

- **Histocompatibility Working Group**
  The NIAID joined several other institutes and the Juvenile Diabetes Research Foundation in supporting the Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in over 70 countries that collect and share data on genes of the human leukocyte antigen (HLA) complex. These are the genes that encode the surface molecules involved in the immune response. The IHWG studies five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. In addition, the IHWG will launch a project to discover single nucleotide polymorphisms (SNPs) in type 1 diabetes-related genes.

SNPs are naturally occurring genetic variations that may be used to identify the genes underlying susceptibility to type 1 diabetes. To date, SNP data have been gathered for over 100 immune response-related genes. More information about the IHWG can be found on their website at *http://www.ihwg.org*.

- **North American Rheumatoid Arthritis Consortium**
  North American Rheumatoid Arthritis Consortium (NARAC) is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. More information can be found at *http://www.arthritis.org/research/research_program/Targeted_Initiatives/narac.asp* is co-sponsored by the NIAMS and the Arthritis Foundation.

Genetics

In FY 2000, the NIAID joined several other institutes and the Juvenile Diabetes Research Foundation International to support the 13th International Histocompatibility Working Group (IHWG) in cataloging the HLA gene complex. In the process, the consortium will explore the HLA gene complex's differences among populations worldwide in an effort to improve the ability to predict, diagnose, and treat immune-mediated diseases, including type 1 diabetes. The NIAID supports an IHWG project to identify single nucleotide polymorphisms in immune response genes. These variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases.

Outreach

The NIAID's informational brochure, *Understanding Autoimmune Diseases*, enhances the public understanding of the immunologic basis for these diseases and the promise of immunomodulation for the treatment and prevention of these diseases in the future.

General

The NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC), established in FY 1998 at the request of Congress, to increase collaboration among the NIH institutes, other federal agencies, foundations, and voluntary health organizations interested in these diseases. The first report of the ADCC, published in December 2000, provides details on the individual initiatives, sponsors, and on current and planned autoimmune diseases research. The report is located at *http://www3.niaid.nih.gov/about/organization/dait/PDF/ADCC_Final.pdf*. In early 2005, the ADCC will submit its third report to Congress. This report will summarize FY 2003 NIH funding for autoimmune diseases research, and accomplishments and activities, including ongoing research projects and future initiatives that address components of the ADCC Autoimmune Diseases Research Plan. The Research Plan, mandated in the Children's Health Act of 2000 (P.L. 106-310), was presented to Congress in 2002, and highlights opportunities to increase our understanding of autoimmune diseases at the population, individual, and molecular levels, with a focus on the underlying immune mechanisms common to many of these diseases.

Other Research

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS), a condition of unknown cause characterized by chronic debilitating fatigue and frequent subjective constitutional symptoms, has been a subject of NIAID-funded research for almost 20 years. NIAID's long-standing involvement resulted from early theories that CFS might be caused by Epstein-Barr virus (EBV). Additionally, the observation that a number of symptoms of CFS overlap those associated with many infectious diseases led to the suggestion that other infectious organisms might play a role in the etiology or pathogenesis of this disease. To date, no single cause has been found for CFS, nor has any microbiologic, immunologic, or physiologic marker proven to be diagnostic or prognostic. Although a purely infectious

or immunologic cause of CFS now seems unlikely, it is conceivable that infection could trigger CFS through unknown pathways. The eventual understanding of the complex symptomatology of CFS will require continued interdisciplinary research efforts.

Prevalence and incidence rates for CFS have been difficult to obtain for several reasons, including lack of an objective diagnostic criteria, differences in case definitions used by investigators in different countries, and potential biases related to case ascertainment. Given these factors, different estimates have been obtained by different investigators. Current NIAID accomplishments are as follows:

- **CFS Cooperative Research Centers**
  The NIAID has supported these centers to conduct research addressing basic science and clinical and epidemiological aspects of CFS since the early 1990s. These sites support studies examining immunological and cardiovascular issues, and cognitive behavioral stress therapy.

- **Enterovirus RNA and its Relation to Fatigue**
  In FY 2002, the NIAID funded a new study that uses a mouse model to look at enterovirus RNA and its relation to fatigue. Enteroviruses are a sub-group of small viruses from the picornavirus family that typically multiply in the gastrointestinal tract. This application was submitted in response to a NIAID RFA, Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection (*http://grants2.nih.gov/grants/guide/rfa-files/RFA-AI-01-004.html*). (R01 AI051270; Dr. Patricia Tam, University of Minnesota)

- **Activity Intervention for Chronic Fatigue Syndrome**
  The NIAID, in partnership with the National Institute for Nursing Research, is currently co-sponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients. It is hoped that this study will provide important new information about response to treatment and possibly individual host factors that may influence response in CFS. (R01AI49720; Principal Investigator Dr. Jason Leonard, De Paul University)

Initiatives

Request for Proposals (RFPs)

- **Reagent Resource Support for AIDS Vaccine Development**
  This RFP was issued to provide the Vaccine Prevention Research Program of the Division of AIDS with an array of reagents (viral proteins, peptides, monoclonal and polyclonal antibodies, topical microbicides, vaccine adjuvants, cytokines, and any additional reagents) deemed necessary for the DAIDS vaccine program. One contract was awarded to Quality Biological Associates. (RFP-NIAID-DAIDS-03-01)

- **Primate Core Immunology–Virology Laboratory**
  The vaccine and prevention research program of the Division of AIDS is supported by this RFP. This resource will provide support of AIDS vaccine studies in human primates by performing standardized assays to assess both cellular and humoral immune responses of non-human primates to HIV and SIV vaccine candidates. In addition, post-exposure assays will be performed to determine and measure viral replication levels. This reference will serve as Reference Laboratories for Quality Assurance and Quality Control of the immune- and virology-based assays for standardization of assays across the non-human primate AIDS research field. A contract was awarded to Beth Israel Deaconess Medical Center to provide this resource. (RFP-NIAID-DAIDS-03-02)

- **HIV Vaccine Design and Development Teams**
  This RFP was issued to augment the vaccine product pipeline via a focused, development-based approach. Funding is provided for teams to provide a strategic research plan for vaccine development that can redirect the focus based on changing needs and emerging new technologies and knowledge. Three offerors were funded under this RFP: Progenics Pharmaceuticals, Inc., Epimmune, Inc., and Novavax, Inc. (RFP-NIAID-DAIDS-03-12)

- **HLA Typing and Epitope Mapping Relative to HIV Vaccine Design**
  Supporting acquisition of datasets is the purpose of this RFP. These datasets are obtained by studying the immune response of individuals infected with non-clad B HIV-1. The datasets are composed of immune response markers and measurements. Limited information is known about the range and diversity of the genetic and ethnic backgrounds in non-clade B virus-infected populations, and a scientific knowledge gap exists as to how the genetics and ethnicity affects immune response to HIV-1. One contract award was made to the General Hospital Corporation. (RFP-NIAID-DAIDS-03-13)

- **Pharmokinetics and Pharmodynamics of Antimicrobials in Animal Models**
  This RFP was initiated to provide DAIDS with a resource to evaluate novel compounds for physical, pharmacokinetic, and pharmacodynamic properties. (RFP-NIAID-DAIDS-03-21)

- **Regulatory Compliance Center**
  Initiated to operate and manage the Regulatory and Compliance Center, this RFP supports a wide range of clinical research activities and programs administered in the Division of AIDS. The contract was awarded to Technical Resources International, Inc. (RFP-NIAID-DAIDS-03-26)

- **Master Contract for Preclinical Development**
  This RFP was developed to promote the development of novel microbicides for prevention of sexual transmission of HIV in the absence of a vaccine. One contract was awarded to Advanced BioSciences Laboratories, Inc. (RFP-NIAID-DAIDS-04-23)

- **Primate Models to Evaluate HIV Prevention and Therapeutic Strategies**
  This RFP was issued to maintain the Division of AIDS' capability to evaluate microbicides and potential therapies. This resource will be used for: 1) studies of new microbicide or therapeutic approaches where "proof of concept" in a primate model would provide critical information to advance development; 2) studies that cannot be addressed in other animal models of HIV infection for lack of appropriate viral or cellular target; 3) candidates/strategies in an advanced stage of development that require optimization; and 4) confirmatory studies of candidates/strategies that have proven promising in other animal models of HIV infection. Contracts were awarded to the University of Washington and Southern Research Institute for a period of 7 years beginning September 2001. (RFP-NIAID- DAIDS-01-17)

- **Simian Vaccine Evaluation Units**
  The primary purpose of this RFP is to provide non-human primates for immunization with candidate SIV or HIV vaccine. (RFP-NIAID-DAIDS-01-04)

- **HIV Microbicide Design and Development Teams**
  This RFP for the newly established, milestone-driven program was released with an anticipated FY 2005 award date. The contracts will support streamlined development of microbicide candidates, emphasizing combination products with multiple active agents. Initiation of a Phase I safety trial is required within the award period.

- **Sexually Transmitted Infections Clinical Trials Group (STI CTG)**
  Issued June 13, 2003, this FY 2005 initiative is the first recompetition of the Sexually Transmitted Clinical Trials Unit Contract (RFP-NIH-DMID-97-07). (RFP-NIAID-DMID-04-09)

Request for Applications (RFAs)

- **International Studies of AIDS-associated Co-infections (ISAAC)**
  This RFA was issued to conduct clinical studies in an international setting relating to co-infections with HIV endemic among adults and children in resource-poor tropical zones. Long-term objectives of this RFA are to develop effective and sustainable clinical management strategies that improve local standards of care and to foster research integration for HIV and relevant co-pathogens. (RFA-AI-03-036)

- **Center for HIV/AIDS Vaccine Immunology (CHAVI)**
  Designed to create an extramural HIV/AIDS vaccine center similar to NIAID's VRC, whose sole focus is HIV/AIDS, this RFA will expand research addressing the immunological barriers and the design and evaluation of adjuvants and vaccines to induce mucosal and/or persistent anti-HIV-specific immunity. (RFA-AI-04-051)

- **Sexually Transmitted Infections and Topical Microbicides Cooperative Research Centers (STI TM CRCs)**
  Released August 25, 2003, this RFA is a recompetition of the Sexually Transmitted Diseases Cooperative Research Centers (RFA-NIH-AI-98-007) that will refocus and expand the CRCs in order to develop better approaches for the diagnosis, prevention, and treatment of STIs. (RFA-AI-03-042)

- **Microbicide Preclinical Development Program**
  Awards were made to six program projects submitted in response to this RFA; three of which were funded by the NICHD. The purpose of the RFA is to expand the range of microbicide candidates, with and without contraceptive activity, through support of discovery and preclinical development of novel or underexplored microbicides. (RFA HD-00-018)

- **Gene Therapy Approaches for Diabetes and Its Complications**
  The NIAID, the NIDDK, and the NHLBI issued this RFA to support the development of novel gene therapy approaches for the treatment of diabetes and its complications. This is supported in part from trans-NIH Diabetes Initiative funds. (RFA-DK-01-006)

- **Sex-based Differences in the Immune Response**
  In FY 2002, 14 research projects were funded under this research initiative. In addition, the NIAID, with the NIH Office of AIDS Research and the ORWH, funded a program project to investigate the female genital mucosal immune response. While differences in the immune response of males and females have been documented, including: the increased incidence of autoimmune diseases in women; pregnancy-induced changes in immune-mediated diseases; and differences in the rate and severity of infection, the reasons are unclear. Increased understanding of the mechanisms underlying the differences in the immune response in males and females should allow more targeted approaches at prevention and treatment of disease. Co-sponsors include the NIAMS, the NINDS, the ORWH, and the National Multiple Sclerosis Society. (RFA AI-01-005)

- **Non-human Primate Transplantation Tolerance Cooperative Study Group**
  The NHPCSG was established in FY 1998 to develop novel approaches to tolerance induction and to evaluate the safety and efficacy of tolerogenic regimens in large animal models of kidney and islet transplantation. In FY 2002, the number of centers was increased to ten and a monkey breeding facility was expanded. To date, study group scientists have demonstrated long-term graft acceptance in both kidney and islet transplant recipients. (RFA-AI-01-006)

- **Sexually Transmitted Infections and Topical Microbicides Cooperative Research Centers (STI TM CRCs)**
  This FY 2004 initiative, released August 25, 2003, was a recompetition of the Sexually Transmitted Diseases Cooperative Research Centers (RFA-NIH-AI-98-007) that refocused and expanded the CRCs in order to develop better approaches for the diagnosis, prevention, and treatment of STIs. (RFA-AI-03-042)

- **Hyperaccelerated Award/Mechanisms in Immunomodulation Trials**
  The NIAID, the NIAMS, the NIDDK, the NINDS, and the NIDCR support investigator-initiated research applications for mechanistic studies in clinical trials of: 1) immunomudulatory interventions for immune system-mediated diseases including, but not limited to, asthma and allergic diseases; graft failure in solid organ, cell, tissue, and stem cell transplantation; and chronic inflammatory, autoimmune, and immunodeficiency diseases; and 2) preventative and therapeutic vaccines for non-HIV/AIDS infectious diseases, including

NIAID Category A, B, and C agents of bioterrorism and emerging/re-emerging infectious diseases. (RFA-AI-04-001)

- **HLA Region Genetics in Immune-mediated Diseases**
  The NIAID invites applications from single institutions or consortia of institutions to participate in a cooperative research group to define the association between human leukocyte antigen region genes or genetic markers and immune-mediated diseases, including risk and severity of disease, and organ, tissue, and cell transplantation outcomes. (RFA-AI-04-039)

Program Announcements (PAs)

- **Enrolling Women and Minorities in HIV/AIDS Research Trials**
  This PA was issued to study innovative strategies that will help in improving the enrollment of women and minorities in HIV/AIDS research trials. Two grants have been funded through the NINR, a co-sponsor of this PA, in response to this PA. (PA-03-168)

- **Novel HIV Therapies: Integrated Preclinical/Clinical Program**
  This initiative was designed to maintain a strong and diverse base in preclinical discovery and development of potential new therapeutics and support the translation of innovative treatment concepts from preclinical studies to pilot clinical proof of concept studies. (PA-03-138)

- **Integrated Preclinical/Clinical Program for Topical Microbicides** (PA-03-137)

- **HIV Vaccine Research and Design Program (HIVRAD)**
  This PA was designed to accept projects beyond the exploratory Innovation Grant Program, but lacking the advancement for the product/clinically oriented IPCAVD program. Several awards were funded by the NIAID. (PA-03-094)

- **Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) Program**
  This PA is intended to support multi-project HIV vaccine design and development research. Research must be product development and late-stage vaccine optimization which must include limited human studies. One award was funded through this PA. (PA-03-095)

- **Centers for AIDS Research: D-CFAR, CFAR**
  This is a PA re-issue whose objective is to provide funding for support of a multidisciplinary environment that promotes basic, clinical, epidemiological, behavioral, and translation research in the prevention, detection, and treatment of HIV infection and AIDS. Eight awards have been made through this PA. (PA-03-089)

- **Innovation Grant Program: Approaches in HIV Vaccine Research**
  This PA was issued to support research projects that are innovative, novel, considered high risk/high impact, and exhibit the potential to advance AIDS prophylactic vaccine design or evaluation. Support is intended to generate preliminary data for further studies. Sixteen grant applicants have been provided funds through this PA. (PA-03-082)

- **National Cooperative Drug Discovery Groups for Tuberculosis (NCDDG-TB)**
  The purpose of this PA is to support a multidisciplinary program projects grants with adequate preliminary data for serious development of new therapies to treat tuberculosis, a prominent deadly AIDS-associated co-infection in Africa, Asia, and Eastern Europe. (PA-03-028)

- **HIV Pathogenesis in Women's Interagency HIV Study (WIHS)**
  The NIAID, along with six other NIH institutes and the NIH ORWH, invited applications for highly focused basic research integrated with the WIHS scope and structure. Applications are expected to utilize the WIHS study population, a large cohort of HIV-infected women in the United States, to formulate specific hypotheses concerning HIV/AIDS pathogenesis in women. The WIHS cohort is followed in five large metropolitan areas —New York, Washington, DC, Chicago, Los Angeles, and San Francisco. (PA-97-105)

- **Statistical Methods in HIV/AIDS Research**
  The NIAID and the National Institute of Mental Health invited applications for the development of original statistical methods to advance the understanding, treatment, and prevention of human immunodeficiency virus disease/AIDS. (PA-98-054)

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides**
  Co-sponsored with the NICHD, this PA is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations, and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segue these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network. See *http://grants.nih.gov/grants/guide/pa-files/PA-01-084.html* for more information. (PA-01-75)

- **Innovation Grants in AIDS Research**
  This PA was released to stimulate new, scientifically challenging, and untested ideas into AIDS research with a particular focus on microbicide research. In brief, applications were encouraged in several areas of new approaches for microbicides, including viral and cellular processes involved in the transmission, local propagation, and spread of HIV; processes for cervicovaginal and rectal transmission of HIV; improved methods of formulation and delivery; and preclinical systems to test microbicide safety and efficacy. Several awards were made for novel microbicide strategies and delivery systems. (PA-02-046)

- **Innovative Grants for Research in Human Immunology**
  The NIAID, the NCI, the NICHD, and the NIDCR invited applications to test novel approaches for elucidating the biology of the human immune system. (PA-02-073)

Conferences and Workshops

- **External Scientific Review Panel**
  This panel of outside experts was convened on May 15, 2003 in Bethesda, MD, to review a proposed trial, designated HPTN 035, to be conducted within the HIV Prevention Trials Network (HPTN). HPTN 035 is a Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5 Percent PR02000/5 Gel (P) for the Prevention of HIV Infection in Women. The overall charge to the panel was to advise whether:

  – the study products were appropriate for testing in an advanced clinical trial; and

  – the scientific/statistical design of the protocol was sound and feasible for the planned study sites.

  The panel's recommendations confirmed the merit of the trial proposed in the context of the current status of the microbicide pipeline and underscored the likelihood of achieving the proposed objectives at the selected study sites.

- **Topical Microbicides Development and Evaluation Workshop**
  The first joint meeting of DMID-, DAIDS-, and NICHD-supported investigators with Topical Microbicide P01s and U I9s was held March 18-20, 2003. The workshop focused on issues ranging from basic research through formulation and applicator design and served as a forum for establishing collaborations among STI and HIV investigators in the microbicide arena.

- **Recent Progress in and Potential Future Direction for Research Related to Environmental Influences on Autoimmunity and Autoimmune Diseases Workshop**
  On February 4-5, 2003, the NIAID, in cooperation with the NIEHS, the NIAMS, the NIH ORD, the NIH ORWH, the American Autoimmune Related Disease Association, and the U.S. Environmental Protection Agency, organized a workshop to discuss recent progress in and potential future direction for research related to environmental influences on autoimmunity and autoimmune diseases. Plenary presentations at the workshop highlighted recent studies in epidemiology of autoimmune diseases, gene-environment interactions, and immunological effects of environmental chemicals.

- **Current Status of the Specimens and Information Collected by the MADGC**
  On February 24, 2004, the NIAID hosted a panel of experts in disease gene mapping to review the current status of the specimens and information collected by the MADGC. The panel commended the consortium on its efforts and recommended a detailed analysis of a subset of specimens in the repository to assess the potential value of the resource.

- **Human Leukocyte Antigen (HLA) Genetics in Immune-mediated and Infectious Diseases Expert Panel**
  Convened on March 2-3, 2004 by the NIAID, this expert panel consisted of 18 leading HLA geneticists to discuss progress in understanding the role of HLA region genetics in a variety of immune-mediated and infectious diseases, and to set priorities for future research in these areas.

- **Sex-based Differences in the Immune Response Program Meeting**
  On September 14, 2004, the NIAID convened a plenary meeting in Bethesda of principal investigators from the grants funded under RFA AI-01-005, Sex-Based Differences in the Immune Response, and representatives from the RFA co-sponsors (the NIAID, the NIAMS, the National Institute of Neurological Disorders and Stroke, and the National Multiple Sclerosis Society). Investigators presented research updates and discussed resources, collaborations, and future directions.

- **The Rectal Microbicide Workshop**
  This workshop was held June 7-8, 2001, in Baltimore, MD, to review the overall state of knowledge in this field, and identify what important research questions must be addressed to make progress in developing and deploying additional methods to reduce the risk of HIV transmission during anal sex. Breakout sessions were focused on several key areas:

  - What is the potential and what are mechanisms for stimulating industry involvement?
  - How can we advance from concept to candidates?
  - What are appropriate aims and endpoints of Phase I/II trials?
  - What are the principal design features for a rectal microbicide efficacy trial?
  - In addition to providing an overview of the state of the art in this field, the workshop provided an opportunity to develop the multidisciplinary interactions necessary to advance rectal microbicide development.

- **The Topical Microbicides Pre-Clinical Workshop III**
  Held in Baltimore, January 31-February 1, 2001, the primary goal of the workshop was to assess the state of current knowledge about pre-clinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV. The workshop also served to: 1) review the progress of the Topical Microbicide Program Projects; 2) facilitate collaborations among scientists from different disciplines and among academic and private-sector participants; and 3) encourage interactions between FDA regulatory staff and commercial sponsors. Scientists from the public and private sectors, representatives from industry, government staff with responsibility for research programs and regulatory activities, foundation representatives, and members of the topical microbicide advocacy community attended the workshop.

- **Topical Microbicides Program Project Reverse Site Visit**
  Formerly known as the Pre-clinical Topical Microbicides Workshop, this workshop was held in Washington, DC, January 9-10, 2002. The primary goal of the site visit was to assess the progress of research conducted by the Topical Microbicide Program Projects toward the pre-clinical development and evaluation of candidate products for preventing sexual transmission of bacteria, protozoa, and viruses, including

HIV. Scientists from all projects of the six DMID-supported Topical Microbicide Program Projects, principal investigators of six newly funded Microbicide Preclinical Development Program projects (DAIDS and NICHD), representatives of government staff with responsibility for research programs, and several external reviewers attended the site visit. The overall consensus of the reviewers was communicated to the Principal Investigators.

- **NIH Working Group on HPV**
  The NIAID, in collaboration with the NCI, continues to participate in the NIH Working Group on HPV. The purpose of the group is to share information, coordinate research efforts, and explore possible collaborative efforts in the NIH HPV research program.

- **CFS Research Across the NIH**
  A trans-NIH working group was established in the NIH OD (coordinated by the ORWH) to coordinate and stimulate new CFS research across the NIH. This group replaces the former NIH CFS Coordinating Committee.

- **Trans-NIH Topical Microbicide Working Group**
  A trans-NIH Topical Microbicide Working Group was established in the NIH OD to coordinate and plan for topical microbicide research. The group meets periodically.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiologic research, research training, and information programs on many of the more debilitating diseases affecting Americans. The NIAMS supports research on a number of diseases disproportionately affecting women, including: osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint disorders (TMJ), fibromyalgia, and systemic lupus erythematosus (lupus). Lupus is a disease 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.

Accomplishments

Osteoarthritis

Osteoarthritis, or degenerative joint disease, is the most common form of arthritis. It is a slowly progressing disease characterized clinically by pain, deformity, enlargement of the joints, and limitation of motion. The disease usually occurs late in life and most commonly affects the hand and large weight-bearing joints. Approximately 20.7 million adults have physician-diagnosed osteoarthritis. Additionally, more women than men suffer from severe osteoarthritis and African Americans have higher rates of hip and knee osteoarthritis.

Enrollment Begins for Osteoarthritis Initiative

In 2001, the NIAMS and the NIA joined with several other institutes and centers and four pharmaceutical companies, in launching the Osteoarthritis Initiative (OAI), a public-private partnership aimed at developing clinical research resources that support the discovery and evaluation of biomarkers and surrogate endpoints for osteoarthritis clinical trials. Four clinical sites and one data coordinating center were selected to establish and maintain a natural history database that will include clinical evaluation data and radiological images, and a biospecimen repository. Patient recruitment is actively underway and by the end of FY 2004, more than 1,000 patients had been recruited. Ultimately, results from the OAI may enable doctors to use biological markers to help identify people at risk for osteoarthritis and people with osteoarthritis at risk for disease progression. Additional support for the OAI is provided by the NIH Office of Research on Women's Health (ORWH).

Osteoarthritis Biomarkers Network: A New Way to Study Disintegrating Joint

To hasten the pace of discovery of molecular biomarkers for osteoarthritis, the NIAMS has established the Osteoarthritis Biomarkers Network. The network includes five institutions in the United States and Sweden. For the first

time, researchers who have been individually studying osteoarthritis biomarkers—molecular indicators of disease presence and progression—are sharing clinical, biological, and human resources. Through the network, investigators will learn more about joint destruction by identifying and monitoring biomarkers in joint, bone, and synovial tissues. This could provide the clues needed to define the stages of disease on a more consistent and reliable basis.

Using Chopsticks: A Risk Factor for Osteoarthritis in the Hand

Using chopsticks contributes to osteoarthritis in the hand, according to researchers studying elderly Chinese individuals. Chopstick use puts stress on certain joints, specifically joints of the thumb and second and third fingers. X-rays of the subjects' hands showed osteoarthritis in those joints, even if the subjects reported no pain. Women, more than men, showed a higher prevalence of osteoarthritis in several joints of the fingers of the chopstick hand, compared to the non-chopstick hand. Researchers attribute the higher prevalence in women to the fact that women generally develop more hand OA than men. Interestingly though, OA in both men and women was less prevalent in the joint at the base of the thumb. Apparently, holding chopsticks puts little stress there, offering a protective effect on that particular joint.

Acupuncture Relieves Pain and Improves Function in Knee Osteoarthritis

In recent years, scientific inquiry has begun to shed more light on acupuncture's possible mechanisms and potential benefits, especially in treating painful conditions such as arthritis. In this study a multisite study team, including rheumatologists and licensed acupuncturists, enrolled patients age 50 or older with osteoarthritis of the knee. Participants were randomly assigned to receive one of three treatments: acupuncture, sham acupuncture, or participation in a control group that followed the Arthritis Foundation's self-help course for managing their condition. Patients' progress was assessed at 4, 8, 14, and 26 weeks. By week 8, participants receiving acupuncture were showing a significant increase in function and by week 14 a significant decrease in pain, compared with the sham and control groups. These results, shown by declining scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), held through week 26. Overall, those who received acupuncture had a 40 percent decrease in pain and a nearly 40 percent improvement in function, compared to baseline assessments.

Osteoporosis

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 United States 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.

Parathyroid Hormone and Alendronate: Combining Treatments Shows No Bone Density Advantage

Combining the bone-building treatment parathyroid hormone (PTH) with alendronate, a drug that slows bone loss, produces no significant improvement in bone mineral density (BMD) beyond that produced by the individual drugs, according to two new studies involving postmenopausal women and men with low BMD. Although clinicians had hoped to optimize osteoporosis treatment and increase BMD by combining the two potent medications, the two trials show that PTH alone increases BMD at least as well as or better than combination therapy. Further studies, say some scientists, are needed to see if the optimal effects of these drugs might be achieved by sequential or cyclic therapy. A comparative study of fracture rates would also be needed to assess drug effectiveness.

Alendronate and Calcitriol Similar in Reducing Bone Loss After Heart Transplantation

NIAMS-supported researchers testing the effects of two bone-active drugs in heart transplant recipients have found that both reduce the degree of bone loss commonly seen in the first year following transplant surgery. The drug alendronate, however, which reduces the

activity of cells that cause bone loss, was judged to be more clinically useful than calcitriol, a synthetic substance similar to vitamin D, which helps regulate calcium metabolism in the body. The results point to the value of treating bone loss in transplant patients.

Homocysteine Level Predictive of Fracture Risk in Older Persons

Elevated levels of homocysteine are found in people with homocystinuria, an inherited metabolic disorder. Since people with homocystinuria are at an increased risk for osteoporosis, researchers hypothesized that other people with elevated blood levels of homocysteine might also be at risk. An analysis revealed that men and women with the highest homocysteine levels were at greater risk for hip fracture, as compared to those with the lowest levels. The risk was increased fourfold in men and twofold in women, and it was independent of other risk factors for fracture, such as age and weight. Levels of homocysteine are elevated in people who don't get adequate amounts of folic acid and other B vitamins (B6 and B12), and getting enough of these vitamins can significantly lower homocysteine levels. The authors suggest that increasing one's intake of folic acid and other B vitamins may result in a reduced risk of fracture. This hypothesis remains to be tested, however.

Inhibiting Enzyme Increases Bone Density

Researchers have used a combination of mouse breeding and genetic technology to identify a gene that strongly influences peak bone mass in mice. The Alox15 gene, which is present in humans as well as mice and is responsible for the production of the enzyme 12/15-lipoxygenase (12/15-LO), was not previously known to be involved in bone biology. In a further phase of the study, the researchers investigated the effect of pharmacological inhibitors of the 12/15-LO enzyme. These drugs had already been developed to inhibit 12/15-LO in other conditions, such as atherosclerosis (clogged arteries), cancer, and asthma, in which this enzyme is also thought to play a role. The use of these drugs resulted in an increase in BMD throughout the body in mice that were estrogen-deficient after removal of the ovaries. Reduction in estrogen production with menopause is the major cause of loss of BMD during later life.

Rheumatoid Arthritis

In rheumatoid arthritis, the immune system, for unknown reasons, attacks a person's cells inside the joint and results in pain, swelling, stiffness, and loss of function. Scientists estimate that 2.1 million people, or 1 percent of the U.S. adult population, have rheumatoid arthritis. The disease occurs two to three times more often in women than in men.

New Study to Show How Rheumatoid Arthritis Patients Rate Improvement Change

A new clinical study, The Clinically Important Changes in Rheumatoid Arthritis, will determine how people with rheumatoid arthritis evaluate improvements in disease symptoms. Researchers in the intramural program at the NIAMS will examine how much of an improvement in pain, stiffness, function, and other symptoms is needed before patients consider the change important. The results of this study will give doctors a measure of the degree of improvements in symptoms and signs of arthritis that patients think are important. This will provide a target to be used in evaluating new treatments. Using these patient-based criteria, doctors will know if a new treatment has a high likelihood of being rated by patients as helpful or not.

Study Shows Reduced Disability for People with Rheumatoid Arthritis

During the past 20 years, significant changes in managing rheumatoid arthritis have taken place. New and more powerful drugs are standard, and treatment with these new drugs is more aggressive. These treatment strategies have improved short-term disability outcomes, but long-term trends in disability had not been studied until recently. NIAMS-supported researchers found that average disability levels in patients with rheumatoid arthritis have declined by 40 percent since 1977 at a rate of about 2 percent per year. The scientists used data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) data bank. The data bank is large, with treatment history for a broad

range of patients, and contains measurements of disability that are widely accepted, including the ability to perform such daily activities as dressing, eating, and walking. The study's timeframe corresponds to the period during which the use of the drug, methotrexate, became a standard treatment for rheumatoid arthritis.

Coffee and Tea Not Risk Factors for Rheumatoid Arthritis

Contrary to previous reports, drinking four or more cups of coffee a day does not put women at risk for developing rheumatoid arthritis. Recently, NIAMS-supported researchers have concluded that there is little evidence to support a connection between consuming coffee, decaffeinated coffee, or tea and the risk of rheumatoid arthritis among women. Researchers used the Nurse's Health Study, a long-term investigation of nurses' diseases, lifestyles, and health practices, to examine possible links between the beverages and rheumatoid arthritis risk. The researchers were able to followup more than 90 percent of the original pool of participants who answered a 1980 food frequency questionnaire, and no links were found. They also considered changes in diet and habits over a prolonged period of time, and when the results were adjusted for other factors, such as cigarette smoking, alcohol consumption, and oral contraceptive use, the outcome still showed no relationship between beverage consumption and risk for rheumatoid arthritis. Previous research had suggested an association between consuming coffee or decaffeinated coffee and rheumatoid arthritis risk. The data supporting that conclusion were inconsistent. Because the information in the older studies was collected only at one point in time, consideration was not given to other factors associated with rheumatoid arthritis, such as cigarette smoking and other possible changes in diet and lifestyle over a follow-up period. The new study presents a more accurate picture of beverage consumption and rheumatoid arthritis risk.

Scientists Find Markers for Rapid Progression of Rheumatoid Arthritis

NIAMS-supported researchers have identified markers that are early indicators of progressive disease in rheumatoid arthritis. Scientists found that the following factors, present at disease onset, predict x-ray evidence of fast progression: older age; bone that has worn away (erosions); rheumatoid factor, an antibody in the blood; rheumatoid factor titer, measurement of amount of rheumatoid factor in reaction with a specific testing medium; variations in specific genes related to immune function and to the protein uterglobin; and T cells (CD4+,CD28null) associated with an aging immune system. The study's findings suggest that more appropriate treatment strategies could be based on likely disease course, and underscore the need for further investigation.

Synthetic Peptide May Help Correct Damaging Immune Responses in Rheumatoid Arthritis

Researchers supported by the NIAMS have found a potential treatment to suppress the abnormal, self-directed immune response that is responsible for rheumatoid arthritis without hampering the body's ability to fight bacteria and viruses. The treatment is a synthetic peptide—a chain of amino acids—called dnaJP1. Previously, researchers had found that in rheumatoid arthritis the immune system is confused by a sequence of amino acids, called leuokcyte antigen (HLA), produced on cells' surfaces during an immune response. In many patients with rheumatoid arthritis, HLA shares a specific characteristic sequence of amino acids. In healthy people, HLA works to help keep the body's immune response under control, but in rheumatoid arthritis, the antigen fails to work properly, resulting in an immune response that causes damage. To help prevent that damaging response, researchers focused their study on the protein called dnaJP1 that the body uses to initiate the response. A particular section of that protein—dnaJP1 peptide—has the same characteristic amino acid sequence as that found in patients with rheumatoid arthritis. By giving patients a synthetic version of the dnaJP1 peptide, the researchers suspected they can teach the immune system to tolerate this specific amino acid chain instead of seeing it as foreign and attacking it. In an initial study in a group of patients with rheumatoid arthritis, blood tests showed that dnaJP1 resulted in normal immune system responses. The results of this initial study form the basis of a new larger study that will also assess patients' symptoms and evaluate

the effects of dnaJP1 on the immune system and physical exams to determine if changes in the immune system result in a reduction in symptoms.

Genetic Variation Found to Double Rheumatoid Arthritis Risk

Scientists have long suspected that autoimmune diseases, such as rheumatoid arthritis, result from a combination of genetic and environmental factors. A research team, partially funded by the NIAMS, working to understand the genetic aspect of rheumatoid arthritis has identified one culprit: a specific genetic variation, called a single nucleotide polymorphism (SNP), that increases RA risk twofold. The SNP is located within a gene that codes for an enzyme called PTPN22. The enzyme is known to be involved in controlling the activation of white blood cells, called T cells, that play an important role in the body's immune system. Under normal conditions, the enzyme works as a negative regulator: it inactivates a specific signaling molecule which, in turn, interrupts the communications and keeps immune cells from becoming overactive. However, in cases where the SNP is present in one or both copies of a person's genes for this enzyme, the team found that the negative regulation by the enzyme appears to be inefficient, allowing T cells and other immune cells to respond too vigorously, causing increased inflammation and tissue damage. Additional support for this study was provided by the ORWH.

Temporomandibular Joint Disorders

Temporomandibular joint (TMJ) disorders are a heterogeneous group of chronic pain conditions involving the temporomandibular joint and/or surrounding musculature, including the muscles of mastication. While pain is the primary symptom of these disorders, there are indicators that have been used to reflect potential underlying pathology, which may occur with or without pain. Studies suggest that TMJ disorders are more prevalent in the young and in women.

Gender Differences in Pain Sensitivity

According to research completed by NIAMS-supported investigators, women are more sensitive to experimental pain than men. Researchers evaluated patient responses to a stimulus that was applied to the finger across a series of repetitions. Overall, women reported higher levels of unpleasantness and pain intensity than men. This research has provided new information regarding the perception of, and response to, painful stimulation and pathological pain which could help to explain the higher prevalence of various chronic pain conditions among women, including TMJ. This study is supported by the NIAMS and is part of the ORWH's Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health.

Initiatives

Request for Applications (RFAs)

- **Osteoarthritis Biomarkers Network**
  The purpose of this RFA, issued in February 2003 by the NIAMS, was to encourage the submission of applications from qualified investigators interested in research and development projects designed to identify and characterize biochemical markers to assess OA disease risk, onset, progression, and response to treatment. Investigators in the network work collaboratively and share resources for the development, evaluation, and validation of biochemical markers for OA onset, severity, progression, and response to treatment. (AR-03-006)

- **Gene Expression Studies in Arthritis and Musculoskeletal and Skin Diseases**
  This solicitation, issued in December 2002 by the NIAMS, was to encourage research that focused resources on specific biological and medical problems for which the immediate application of comprehensive gene expression analysis technology has the potential to yield significant new insights. For example, characterizing gene knockout or transgenic mouse strains, in which genetic variation from controls is limited and known, should produce manageable datasets, and may indicate the downstream targets of inactivated or introduced genes. (AR-03-007)

- **High-risk Arthritis and Musculoskeletal and Skin Disease Research**
  The purpose of this RFA, issued in January 2003 by the NIAMS, was to broaden the base of inquiry in fundamental biomedical and biomedical technology research by encouraging research that involves an especially high degree of innovation and novelty and, therefore, requires a preliminary test of feasibility. (AR-03-009)

- **Mechanisms of Mineralization of Bone**
  The purpose of this RFA, issued by the NIAMS in September 2003, was to stimulate and support investigation of the mechanisms that mediate and regulate the incorporation of mineral into bone. Recent observations have underscored the critical contribution of bone mineral to the mechanical properties of bone, including its resistance to fracture. Thus, an improved understanding of the mineralization process could lead to new therapeutic and preventive interventions for reducing the risk of fracture in groups at risk because of bone loss. (AR-04-001)

- **High-risk Arthritis and Musculoskeletal and Skin Diseases Research**
  The purpose of this RFA, issued in October 2003 by the NIAMS, was to broaden the base of inquiry in fundamental biomedical and biomedical technology research by encouraging research that involves an especially high degree of innovation and novelty and, therefore, requires a preliminary test of feasibility. (AR-04-002)

- **The Role of Innate Immunity in Autoimmune Rheumatic Disease**
  The purpose of this RFA, issued in September 2003 by the NIAMS, was to encourage research to increase our understanding of the role of innate immunity in the etiopathogenesis of autoimmune rheumatic diseases. Understanding the role of the innate immune system in the earlier events of the etiopathogenesis of autoimmune diseases could lead to prevention of end organ damage and earlier intervention in autoimmune rheumatic diseases. (AR-04-003)

- **Research on Crystal Deposition Arthropathies**
  The purpose of this RFA, issued in December 2003 by the NIAMS and the NIA, was to invite applications for research on improved diagnosis and treatment of the major crystal deposition arthropathies including gout, calcium pyrophosphate dihydrate (CPPD) crystal deposition disease, and hydroxyapatite crystal deposition disease (also known as basic calcium phosphate crystallopathy). Disease prevalence is increasing among elderly women along with increased longevity, and may be linked to the common use of diuretics and chronic renal insufficiency in this population. Reduced estrogen levels in postmenopausal women may also play a role, as estrogen prevents the formation of new uric acid crystals in the blood. (AR-04-006)

- **Hyperaccelerated Award/Mechanisms for Immunomodulation Trials**
  Issued in November 2003 by the NIAID, the NIAMS, the NIDCR, the NIDDK, and the NINDS, this RFA encouraged mechanistic studies in clinical trials of immunomodulatory interventions of immune system-mediated diseases. These include asthma and allergy; graft failure in solid organ, tissue, cell, and stem cell transplantation; and autoimmune diseases. (AI-04-001)

Program Announcements (PAs)

- **Bone Anabolic Hormones: Their Receptors and Signal Transduction Pathway**
  The NIDDK, the NIA, the NCI, the NIAMS, and the NIDCR released this PA in October 2002 to elicit grant submissions that focused on systemic hormones, local growth factors, and bone-active cytokines with potential bone anabolic effects. Although the primary focus is on basic research, the long-term objective is to identify potential targets of therapeutic value in the treatment of diseases that adversely affect bone, including, but not limited to, osteoporosis due to loss of gonadal steroids, aging, use of glucocorticoids and immunosuppressive drugs, hyperparathyroidism, excessive

thyroid hormone replacement, or tumor metastasis to bone. (PA-03-008)

- **Biobehavioral and Pain Research**
  In July 2003, the NINR, the NIA, the NIAMS, the NCI, the NICHD, the NIDCR, the NINDS, the NIDA, the NIMH, and the NCCAM supported this PA which encouraged researchers to study individual differences in pain responses that may be due to factors such as genetic differences, endocrine activity, neural activity, immune function, psychological state, developmental stage, cognitive capacity, disability state, age, gender, social context, and cultural background. The pain experience needs to be examined at all levels of research, including the gene, molecule, cell, organ, and individual with the goal of developing biobehavioral interventions to manage or prevent pain. (PA-03-152)

- **Aging Musculoskeletal and Skin Extracellular Matrix**
  The NIA, the NIAMS, and the NICHD supported this PA, released in September 2003, to solicit grant applications for basic research projects to investigate how changes in the extracellular matrix with age affect the function of the tissues of the musculoskeletal system and skin. Projects were encouraged that determined how cellular aging processes lead to altered matrix production and maintenance, and how aging-related altered matrix composition and organization affect the function of these tissues. (PA-03-167)

Workshop

- **Fibromyalgia Workshop: The New Advances**
  This workshop, held November 11-12, 2004, summarized and then challenged existing knowledge of fibromyalgia to propose an interdisciplinary research agenda to advance the understanding of its causes and contributing factors. The primary focus was to examine the emerging understanding of the role of non-nociceptive central pain of fibromyalgia. The workshop also provided clinicians with a conceptual grounding of current state-of-the-science understanding of factors contributing to fibromyalgia. Young investigators or investigators new to the field of fibromyalgia received career enhancement opportunities and information.

Health Disparities among Special Populations of Women

Systemic Lupus Erythematosus

Lupus is an autoimmune disease that mainly affects women of childbearing age. Common symptoms of lupus include painful or swollen joints, unexplained fever, skin rashes, kidney problems, and extreme fatigue. Women are nine times more likely than men to have the disease. It is also three times more common in African American women than in Caucasian women, and is more common in women of Hispanic, Asian, and Native American descent. African American women tend to develop the disease at a younger age and to develop more serious complications than Caucasian women.

- **NIH Launches Study of Hematopoietic Stem Cell Transplantation for Severe, Treatment-resistant Lupus**
  Researchers at the NIAMS and the NCI have launched a 5-year study to see whether a therapy using transplantation of hematopoietic stem cells, blood stem cells found in bone marrow, can produce long-term remission for patients with severe, treatment-resistant lupus. The study will include a basic research component to examine the roles of B and T cells, white blood cells in the immune system, in triggering lupus symptoms.

- **Trial to Test Cholesterol Drug Against Artery Fat Buildup in Children with Lupus**
  Researchers participating in the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythymatosus) project will use statins—drugs used to lower LDL (low-density lipoprotein or "bad" cholesterol) levels—to test their effects against fat buildup in the blood vessels of children with lupus. Pediatric patients with lupus are sometimes affected by this fat buildup, also called atherosclerosis. The researchers hope that the statin treatment will have

preventive effects on the arterial fat buildup that may occur in young lupus patients.

- **Arteries Clog Earlier in People with Lupus**
  People with lupus may develop carotid atherosclerosis (the buildup of fatty deposits in the arteries) at an accelerated rate and independently of many risk factors normally associated with cardiovascular disease. The study examined 197 people with lupus and the same number of matched controls. Risk factors for cardiovascular disease, including family history of heart disease, cholesterol levels, smoking, and hypertension were similar in both groups, but atherosclerosis, as evidenced by carotid ultrasound, was more prevalent in lupus patients. The scientists also found that people with lupus who had the disease longer, had more damage from the disease, and had used less of the immunosuppressive drug cyclophosphamide to treat it were more likely to develop fatty deposits in their arteries.

- **Autoantibodies Precede Disease in Lupus Patients**
  Research completed by NIAMS-supported investigators has revealed that people diagnosed with lupus have autoantibodies in their blood years before the symptoms of lupus appear. The early detection of autoantibodies may help in recognizing those who will develop the disease and allow physicians to monitor them before they might otherwise be noticed. Using many years of previously collected samples from the Department of Defense Serum Repository, researchers compared samples from the lupus patients to samples from those who never developed lupus. When testing early samples from both groups, they found that those with lupus had the autoantibodies in their blood for months to years before symptoms appeared. Some of the autoantibodies, such as antinuclear antibody, had been present longer than others. The lupus autoantibodies tend to accumulate in the blood in a predictable pattern up until diagnosis, when the rate of new autoantibodies slows.

- **Genetic "Signature" Linked to Severe Lupus Symptoms**
  A team of scientists, supported by the NIAMS and other parts of the NIH and the private sector, have discovered a genetic "signature" present in some patients with lupus who develop such life-threatening complications as blood disorders, central nervous system damage, and kidney failure. Using DNA microarrays—small silicon chips that contain tiny amounts of thousands of known genes—to carry out a technique called gene expression profiling, researchers analyzed thousands of genes in the peripheral blood cells of lupus patients and healthy controls. Surprisingly, 14 of the thousands of genes studied were linked to a subset of lupus patients with severe disease. In addition, 161 of the genes studied showed different expression patterns in lupus patients compared with healthy controls. The 14 genes, referred to collectively as the IFN (interferon) expression signature, are turned on by the activity of interferon, a complex family of proteins involved in the regulation of immune responses. The data provide strong support for developing new therapies to block IFN pathways in patients with severe lupus, and the pattern of gene expression in blood cells may be useful in identifying patients most likely to benefit from these new therapies. Gene expression profiling in blood cells may also be useful in identifying disease pathways in other autoimmune and inflammatory disorders. Additional support for this study was provided by the ORWH.

- **Additional Insights into Molecular Mechanisms of Brain Changes in Lupus Revealed**
  Recent research indicates that mice can be induced to produce antibodies to a particular receptor (NMDA) on nerve cells in the brain, as well as have them circulating in the blood. The antibodies do not cause nerve damage unless the blood–brain barrier is broken and the antibodies have access to the brain.

When the blood–brain barrier was broken, these antibodies bound to specific areas in the brain and nerve cell death was demonstrated. Behavioral tests in these mice revealed specific cognitive dysfunction as well. Furthermore, if a drug was given that blocked the brain receptor at the time of the breakdown of the blood–brain barrier, no neuronal damage or apparent cognitive dysfunction was evident. These results have defined a mechanism for the occurrence of neuropsychiatric lupus and the changes can be imaged in the brain noninvasively. This brain receptor is also a promising potential target for therapy. These research findings not only help us to understand the nervous system complications in lupus, but also provide some new therapeutic possibilities for these aspects of lupus that can be very challenging for patients, their families, and their health care providers.

Initiatives

Program Announcement (PA)

- **Health Disparities in Rheumatic, Musculoskeletal, and Skin Diseases**
  The NIAMS, the NEI, and the NIEHS released this PA in January 2003 to promote the design, development, and testing of hypothesis-driven innovative approaches to eliminating health disparities in rheumatic, musculoskeletal, and skin diseases. Attention was focused on potentially modifiable environmental, social, and behavioral factors, and on gene–environment interactions that may underlie ethnic/racial disparities in disease prevalence and outcome. (PA-03-054)

Conferences and Workshops

- **Lupus Today: Research Into Action**
  This scientific conference was held September 5-6, 2003 on the current status and future directions of research on and treatment of lupus. The primary goals of the conference were to inform, energize, and share the excitement about the future of lupus research with patients and their families, physicians, health care workers, scientists, and organizations that were involved in lupus research and outreach. Sponsors of the meeting included the ORWH, the NIAMS, and the DHHS Office on Women's Health. A meeting summary can be found at *http://orwh.od.nih.gov/pubs/lupustoday.pdf*.

- **Lupus Federal Working Group**
  The NIH is enhancing research efforts on lupus through a new Lupus Federal Working Group, the purpose of which is to exchange information and coordinate federal efforts in lupus research and education. The working group, led by the NIAMS, is comprised of representatives from all relevant DHHS agencies and other federal agencies having an interest in lupus. These agencies exchange information on new developments and take advantage of new scientific opportunities in the field of lupus research. The first meeting of the working group was in June 2004.

- **Lupus Biomarkers Working Group**
  In the fall of 2003, the NIAMS intramural program held a meeting to discuss the development and validation of biomarkers of lupus. Participants included a number of clinical and basic scientists from the lupus research community, as well as representatives from the NIH, the FDA, and voluntary organizations. A key focus of the day was discussion of the barriers to biomarker development in lupus. The participants also underscored the need to identify the potential biomarkers for lupus that should be examined, develop methodologies to validate potential biomarkers, identify the infrastructure necessary to identify lupus biomarkers, and develop methods to collect and collate clinical material. It was recognized that biomarkers have significant value in clinical settings in facilitating the development and use of new therapies.

NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the research institutes within the National Institutes of Health (NIH) and was established by law in December 2000. The NIBIB received its first appropriation and grant funding authority in fiscal year 2002. As the NIBIB continues to grow and structure programs, new initiatives are in development to support a variety of scientific areas, including programs aimed at fostering women's health research.

The NIBIB serves as the hub within the NIH for coordination of biomedical imaging and bioengineering efforts. The NIBIB: 1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; 2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; 3) formulates research goals and long-range plans with the guidance of the National Advisory Council on Biomedical Imaging and Bioengineering; and 4) sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

The NIBIB recognizes the significant potential of improved imaging technologies in early disease detection. During FYs 2003 and 2004, the NIBIB funded grant awards that were focused on women's health research or technologies aimed at improving devices for female populations. These projects range from advanced imaging methodologies to new drug delivery systems designed specifically for women's diseases, such as breast cancer and disorders and conditions that predominate in women, including osteoporosis and temporomandibular joint diseases (TMJ). Researchers supported by the NIBIB plan to develop high resolution x-ray grids in mammography to detect breast cancer at its earliest stage, thereby greatly increasing patient survival rates. In addition, NIBIB-funded investigators are working on novel drug delivery treatments that will promote bone resorption for women suffering from osteoporosis.

During FYs 2003 and 2004, the NIBIB significantly increased support of women's health research in the following disease areas: aging, autoimmune disease, cervical cancer, contraception/reproduction, diabetes and diabetes research, epilepsy, HIV/AIDS, heart disease (education, research, and coronary heart disease), lung cancer, stroke, stroke research, and temporomandibular joint disease (TMJ).

Women's Health Research

Dr. Roderic Pettigrew, the first Director of the NIBIB, began his tenure at the NIH in September 2002. Since his arrival, the NIBIB has been working to reorganize the institute to facilitate the support of research in areas of relevance to the missions of the NIH and the NIBIB.

In December 2004, Dr. Anthony Demsey joined the NIBIB as the Director of the Office of Extramural Policy. Under the purview of this office, Dr. Demsey has the responsibility of managing and monitoring all NIBIB activities that specifically focus on women's health research. Dr. Demsey and Ms. Tinera Fobbs direct the efforts of the NIBIB in supporting research on women's health by serving as the institute representatives to the Coordinating Committee on Research on Women's Health.

Accomplishments

Highlighted below are significant NIBIB research accomplishments related to women's health.

Breast Cancer

Breast Cancer Diagnosis by Electrical Impedance Imaging

This project is in the first year of funding. The long-term goal of this project is to develop a new technology to improve the screening for and diagnosis of breast cancer. Non-invasive electrical impedance measurements, made with a handheld probe, have been shown to improve the specificity and sensitivity of

mammography for breast tumor diagnosis in patients with ambiguous mammograms. This non-invasive technology poses no known risks to the subject, and provides a new diagnostic parameter to assess suspicious anomalies.

Quantum Dots Could Guide Surgeons

Nanometer-sized crystals, called quantum dots (QD), may one day assist doctor's efforts to assess and treat cancer patients. Now researchers led by Dr. John V. Frangioni of Beth Israel Deaconess Medical Center and Harvard Medical Center are among the first to explore the medical applications of quantum dots, which are manufactured to emit light at specific wavelengths in response to illumination. When injected into an animal near a tumor, the dots quickly reveal the sentinel lymph node closest to the tumor. The researchers hope that someday the dots will help illuminate the sentinel lymph nodes in breast cancer patients and eliminate the need for multiple biopsies. The QD technique may also improve visualization of cancer cells.

Parallel Detection and Computation for Diffuse Optical Tomography of Breast

The aim of this work is to develop and assess near-infrared, diffuse light imaging schemes for tumor detection and characterization using a combination of experimental, theoretical, and computational tools and techniques. During FY 2003, researchers developed computational schemes to improve the accuracy of three-dimensional (3D) reconstruction, as well as recruiting more high-risk patients for *in vivo* measurements.

Co-registered Image of Breast Tumors by MRI and Optical Spectroscopy

The aims of this research project are: improving the existing MR-coupled TR so that it affords optimal breast tumor near-infrared (NIR) optical imaging quality by increasing resolution, the area of coverage, the dynamic range, and the feature detection ability; optimizing the performance of the diffusive optical tomography (DOT) in order to improve imaging of single and multiple (breast-like) heterogeneities; and obtaining DOT images of human breast tumors using instrumental and theoretical improvements. Currently, improvements to the MR-coupled TR area are in place and the optimizing of the performance of DOT and the obtaining of DOT images of human breast tumors are continuous, ongoing processes.

Digital Mammography High-resolution Flat Panel Imager

This is a Bioengineering Research Partnership between University of Massachusetts Medical School and Lockheed-Martin Corporation aimed at developing and evaluating a new, high-resolution flat panel mammographic imager with variable pixel size using tiled charged-coupled devices (CCD). The NIBIB and the NCI are the granting institutes. It has been discovered that the particular technology for high-resolution detection in digital mammography is applicable to computed tomography of the breast applications. It would appear that the technology under development has broader applications than the original intent of high-resolution digital mammography.

Speckle-free Transmission Ultrasound for Breast Imaging

The goals of this project are: image acquisition and post-processing for the C-scan ultrasound images; preliminary tests with laboratory prototype; redesign and fabrication of a pre-market system suitable for imaging the human breast; and development of an interface mechanism for the C-scan ultrasound camera and the breast. The following achievements have been made: a higher dynamic range CMOS-base ultrasound sensor has been successfully built in early 2004 by Imperium scientists and engineers who serve as system developers for the project; a "dry" Breast Ultrasound Fluoroscopy System prototype has been constructed by Imperium; and a set of imaging performance studies have been performed. One of the measurable and deliverable items is a "dry" speckle-free real-time BUFS system with image acquisition capability.

Breast CT Scanner for Earlier Cancer Detection

Breast cancer is a disease with high incidence in the United States and elsewhere, and population-level methods of fighting this disease are aimed primarily at screening, using mammography for early detection. A team comprised of medical physicists, physicians, mechanical and

electrical engineers, and breast cancer advocates will collaborate on the design of the breast computerized tomography (CT) scanner. The scanner will be built, tested, and optimized at UC Davis over a 3-year period. If breast CT lives up to its enormous potential based on initial imaging, breast cancer would be detectable far before metastasis occurs. While breast CT would probably improve cancer detection in all women, some women may have risk factors (dense breasts, genetic markers, etc.) that particularly warrant screening using breast CT. To date, the computer-aided design of the Bodega scanner is nearly complete.

Haptic Interface—Tele-Diagnostics of Breast Pathology

This research is proposed by a multidisciplinary team comprised of physicians, mechanical engineers, electrical engineers, and computer scientists. The objectives of the research is to test the following two hypotheses: 1) a robotic device with haptic and ultrasound capabilities can accurately examine the human breast, and 2) a physician can remotely and accurately examine the human breast using such a robotic device. Ultimately, such a robotic device could be used to do screening for focused breast exams for patients in remote areas without access to physicians. If the device is successfully validated, it could also be used to train healthcare professionals in breast pathology, including cancer. Because of the incorporation of ultrasound capabilities, examinations by the robotic device might prove to be more accurate than examinations done by the physician's own hand.

Computer-aided Detection for MRI Breast Screening

This project proposes to design, develop, and implement a computer-aided detection system for integrating multiple magnetic resonance imaging (MRI) modalities for early detection of breast cancer in high-risk patients, using structural, dynamic contrast-enhanced and diffusion-weighted MRI, and magnetic resonance spectroscopy. A group of high-risk breast cancer patients, willing to participate in clinical trials, is already in place at the Huntsman Cancer Institute, forming a body of prospective participants for the clinical work proposed. The close participation of clinical radiologists with Dr. Schabel, the principal investigator, will significantly facilitate the algorithmic work by providing the knowledge and expertise in interpreting radiologic images against which algorithms will be tested.

Nuclear Radiology of Breast Cancer

The NIBIB and the NCI co-sponsored the first Workshop on the Nuclear Radiology of Breast Cancer. The overall goal of this workshop was to convene international imaging physicists with a particular interest in breast cancer imaging using functional imaging techniques involving radiotracers. The problems of breast cancer detection, diagnosis, and staging were clarified from the biological, chemical, medical, economic, and state-of-the-art instrumentation perspective. The workshop was held in Norfolk, Virginia, November 16-17, 2002. It immediately followed the combined 30th Annual Institute of Electrical and Electronics Engineers Nuclear Science Symposium and 10th Annual Medical Imaging Conference.

Optical Probe Might Find Missed Breast Cancers

A new technology, developed by scientists at the University of Wisconsin–Madison, will be a "third eye" during breast biopsies and can increase the chance for an accurate clinical diagnosis of breast cancer. Dr. Nirmala Ramanujam and her colleagues have developed a light-sensitive probe that will help doctors spot breast cancer in some of the 70,000 American women each year whose malignancies fail to be detected in needle biopsies. Doctors currently use x-ray or ultrasound to guide the biopsy needle into the sample region. In order to ensure they are doing the biopsy at the right spot, they take up to a dozen tissue samples. The new fiber-optic probe can be threaded down the existing hollow biopsy needle to the tip to help doctors find the right area to sample. The new probe will increase the likelihood that doctors take a sample from the correct site, and the improved optical technology will eventually allow doctors to make immediate diagnoses.

Positron Emission Tomography

Positron emission tomography (PET) is a nuclear imaging modality that makes use of a range of positron-emitting tracers to provide images that reflect different parameters relevant to tumor biology. Tumor cells generally differ from normal cells in many respects, including rates of glucose utilization, proliferation, and protein synthesis. There is an urgent need for improvement in PET instrumentation in order to exploit the full potential of this powerful imaging modality. The goal of this proposed effort is to investigate crystals of a new promising scintillator for PET imaging.

Aging and Osteoporosis

Osteoporosis is a 'silent,' progressive, and debilitating disease characterized by bone loss, thinning cortical bone, and disorganized trabecular bone leading to bone fragility and fracture. The goal of the proposed research is to develop novel materials incorporating magnesium (Mg), zinc (Zn), and F (fluoride) ions in a calcium (Ca) phosphate system (Mg/Zn/F-BCP). Separately, these ions have been associated with bone formation, biomineralization, and osteoporosis therapy. Several methods of preparations were explored to obtain Mg-, Zn-, and F-releasing calcium phosphate matrix. More than 70 different preparations were initially obtained using precipitation and hydrolysis methods. In collaboration with Dr. Carmelita Frondoza, Johns Hopkins University, screening of Mg/Zn/F-BCP compounds prepared based on *in vitro* cell response (principally, proliferative capacity) was performed using a osteoblast-like cell line. Results showed that all the preparations tested (about 40) showed significantly higher proliferative capacity (from 1.5- to fourfold) compared to control.

Reproductive Health

Magnetic Resonance Imaging of Placental Oxygenation

Normal fetal development is directly dependent on adequate transfer of oxygen and nutrients across the placenta. Inadequate placental transfer of oxygen results in fetal hypoxemia that has been associated with alterations in fetal physiology and fetal structure. Low levels of fetal oxygenation represent a major cause of intrauterine growth restriction (IUGR), an abnormality that leads to low birth weight (which accounts for 10 percent of all pediatric health care costs in the United States). The goal of this research project is to determine the feasibility of magnetic resonance (MR) oxygenation imaging in the placenta. This project promises significant clinical impact—availability of a noninvasive *in vivo* method to evaluate placental oxygenation could provide a sensitive and clinically relevant measure of placental function, aiding in the earlier and more specific diagnosis of IUGR, allowing for appropriate intrapartum care. The results obtained to date include initial development of an MR-compatible model of placental insufficiency, development of a novel technique for measurement of umbilical vein oxygenation in an animal model using percutaneous umbilical blood sampling, and implementation of MR sequences for *in vivo* measurement of T1 and T2 tissue relaxation values at 3 Tesla, with empirical quantification of those values in various tissues. In each case, the results can be applied more broadly to studies outside the scope of the current project. Taken together, these elements allow the measuring of changes *in vivo* placental oxygenation non-invasively using MRI, a goal that will be pursued in 2003.

Temporal–Spatial Biomagnetic Fields of the Fetus

The primary goal of this research is the development of an integrated computer environment for the analysis and display of biomagnetic signals recorded from pregnant women, including anatomical information obtained by three-dimensional ultrasound. The major achievement during the last year has been the ability to improve the signal-to-noise ratio of the acquired biomagnetic signals using optimal signal analysis technique. A significant outcome of this has been the reliable detection of fetal ST segments. This has a high potential value since with ECG studies in labor it has been shown that the analysis of fetal ST segment have resulted in high positive predictive value of fetal distress.

Fibroids

Uterine Leiomyoma

The NIBIB and the ORWH co-sponsored the Second NIH International Congress on Advances in Uterine Leiomyoma Research. This collaborative interdisciplinary scientific conference addresses the current status of knowledge related to fibroids and implications of current and ongoing research and clinical studies for their clinical management. The conference was held February 24-25, 2005.

Given the newness of the institute and its corresponding budget, it is notable that the NIBIB spent $7,717,523.00 during FY 2003 and $9,952,520.00 during FY 2004 on women's health research and programs.

Initiatives

In FY 2003 and 2004, the NIBIB participated in a number of initiatives that addressed technology development related to biomedical imaging and bioengineering that may have applications in different disease areas relevant to women's health ranging from bioinformatics development to advances in imaging technology.

Request for Applications (RFAs)

- **Improving Measurement Tools for Sternal Skin Conductance and Hot Flashes (Phase I SBIR)**
  The NIBIB and the NCCAM, in collaboration with the ORWH, co-funded this RFA to invite prospective applicants to conduct research to improve measurement tools or devices for sternal skin conductance. Sternal skin conductance devices have been used to monitor hot flashes, but existing tools are limited in the amount of data that they can collect and their utility under ambulatory conditions. Vasomotor symptoms, including hot flashes and night sweats, are symptoms frequently reported by menopausal women, as well as breast cancer survivors and men undergoing androgen deprivation therapy. Until recently, estrogen and other forms of hormone therapy were used to treat vasomotor symptoms among menopausal women. Recent findings from the Women's Health Initiative do not support hormone therapy as a treatment option for vasomotor symptoms and more people are turning to other means to manage hot flashes, including complementary and alternative medicine therapies. (RFA-AT-05-005)

- **Improvement in Imaging Methods and Technologies**
  The NIBIB funded this RFA to support novel investigations for the purpose of improving and extending methodologies and technologies for biomedical imaging. The primary focus of the research funded is on the technological and methodological advance in human imaging. Biomedical imaging devices have been used to obtain anatomical images, and to provide localized biochemical and physiological analysis of tissues and organs. These approaches have included magnetic resonance, computed tomography, nuclear medicine, optical, ultrasound, EEG/MEG, and other imaging devices. The ability of these devices to provide anatomical images and physiological information has provided unparalleled opportunities for biomedical and clinical research, and has the potential for important improvements in the diagnosis and treatment of a wide range of diseases in women. (EB-03-007)

Program Announcements (PAs)

- **Research on the Economics of Diet, Activity, and Energy Balance**
  The NIBIB, along with the NCI, the NIDDK, the NIA, and the OBSSR, co-funded this PA to solicit projects that enhance the state of the science on the causes of obesity and to inform federal decisionmaking on effective public health interventions for reducing the rate of obesity in the United States. Obesity has become an epidemic with health disparity implications, and is a major focus of public health efforts at the national, State, and local levels. (PA-05-009)

- **Innovation Grants for AIDS Research**
  The NIBIB, the NIAID, the NICHD, the NIDCR, the NIDDK, and the NIMH co-funded this PA to encourage the submission of applications to bring new, scientifically challenging and untested ideas into AIDS research. With the

increasing number of AIDS cases in women, there are a number of critical questions in AIDS research that remain underexplored, and new approaches are needed to make progress in these areas. (PA-02-046)

- **Manufacturing Processes of Medical, Dental, and Biological Technologies (SBIR/STTR)**
  The NIBIB, along with other NIH institutes (the NIA, the NIAAA, the NIAID, the NCI, the NIDCD, the NIDCR, the NIDDK, the NIDA, the NIEHS, the NEI, the NIGMS, the NHLBI, the NIMH, the NINDS, the NINR, the NCRR, the NCCAM, and the NLM), the CDC and the FDA, co-funded this PA in response to Executive Order 13329, signed by President George W. Bush Sr., requiring the SBIR/STTR agencies, to the extent permitted by law and in a manner consistent with the mission of the department, to give high priority within the SBIR and the STTR programs to manufacturing-related research and development (R&D). In an effort to comply with this Executive Order, the NIH, the CDC, and the FDA have expanded their foci by encouraging biomedical research related to advanced processing, manufacturing processes, equipment and systems, and manufacturing workforce skills and protection. By supporting the manufacturing of new biomedical products and the implementation of innovative technologies in medical care, women will have access to products with unsurpassed quality. Lower manufacturing cost for existing and/or new processes will foster a reduction of health care costs for women and society at large, improving the cost effectiveness, quality, and accessibility of the health care system. This outcome is vital in the fight to abolish health disparities among special populations of women. (PA-04-161)

- **Telehealth Technologies Development (SBIR/STTR)**
  The NIBIB funded this PA with the purpose of supporting design and development of novel telehealth instrumentation or technologies that can be applied to a broad spectrum of disorders and diseases. Telehealth is defined by the Federal Communications Commission and by the DHHS Office of Health Promotion and Disease Prevention as "the use of communications technologies to provide and support health care at a distance." Examples include the use of communications to provide patient treatment, often via still images or video, and the exchange and distribution of public health information. (PA-03-030)

Health Disparities among Special Populations of Women

Telehealth Delivery of a Weight Loss Program in Diabetes

Significant obesity and type 2 diabetes are emerging epidemics in the United States. Most people with type 2 diabetes are obese. The highest prevalence of obesity is in non-Hispanic black women. Weight loss improves diabetes outcomes and reduces the need for anti-diabetic medication. Implementation of behavioral weight loss programs in a primary care setting has proven to be a challenge. Internet-based weight loss programs have been shown to be effective; however, access to personal computers is limited among elderly and low-income populations. Additionally, computers require a degree of technical sophistication and access to the Internet poses a barrier for a significant portion of the at-risk diabetes population. A solution is required that offers the benefits of Internet-based weight loss programs without the technical challenges or cost. The primary goal of the study is to explore a home-based telehealth system (Healthium) using an interactive television system. The researchers hope to perform a pilot study in patients with type 2 diabetes to determine whether the Healthium interface improves weight loss and diabetes outcomes relative to standard clinic-based treatment. Since the highest prevalence of obesity is in non-Hispanic black women, it is expected that African American women will constitute a major percentage of patients in the study.

In conclusion, the NIBIB will vigilantly continue to develop and support a research portfolio that champions cutting-edge science in the area of women's health research.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

The National Institute of Child Health and Human Development (NICHD) has a unique role to play in women's health research. Although the institute's mission is to ensure that babies are born wanted, timely, and healthy and that they develop to their full physical, emotional, and cognitive potentials, NICHD-sponsored research spans human growth and development. It starts from before conception and continues through infancy, childhood, and adolescence—all critical stages where the foundations for adult health and healthy women are established and are critically important. Given its mission, NICHD research aims to overcome many of the complex challenges that face women in addition to their children and families.

For instance, NICHD-supported research is shedding light on how fibroids form, providing scientists with the preliminary knowledge that they need to begin developing non-surgical treatments for a condition that affects millions of women. In another study, NICHD scientists have found substances in blood that may predict preeclampsia in pregnant women, a complication that can be fatal. The full extent of this finding may be realized in future research leading to the development of treatments that can prevent or treat the condition before it becomes life-threatening, saving the lives of thousands of women.

Through the NICHD Maternal Fetal Medicine Units Network, researchers showed the remarkable effectiveness of a new progesterone treatment that reduces the risk of preterm birth in women who previously gave birth at less than 37 weeks. This is one of the first major discoveries in this area, despite extensive efforts over decades, and promises to help change obstetrical practice. Because of its far-reaching public health impact, the advance appeared in *Parade Magazine* (2004) as one of the year's leading medical advances and was featured on the front page of the *New York Times* (2003).

NICHD researchers also avidly pursue better outcomes to improve women's health around the globe. One of the most important developments is a new treatment option for women in developing nations to protect their unborn infants from HIV. The inexpensive and simple drug-combination reduces the chance of mother-to-child transmission (MTCT) of HIV to less than 2 percent, similar to that of the more complex and expensive treatment in the developed world. Because of its promise to dramatically reduce MTCT rates, the Thailand Ministry of Public Health adopted this regimen as the standard for prevention of HIV MTCT, and the World Health Organization recommends this treatment as the first choice to prevent MTCT in women who do not need more complex therapies for her own health.

To share these scientific advances in women's health and other women's health information, the NICHD recently launched a new website, Women's Health Research at the NICHD. This new resource dedicated to women's health brings together a variety of information about women's health topics, and about ongoing research projects supported by the NICHD. In addition, it provides information about how to pursue research on women's health. The site also offers access to NICHD news releases, publications, conference and event schedules, and other information related to women's health (*www.nichd.nih.gov/about/womenhealth/women_health.cfm*).

The NICHD's advances in women's health are as wide-ranging as the institute's women's health portfolio. This includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are key to improving the quality of life for women.

Accomplishments

Women's Health Research

Since women's health is an integral component of the NICHD mission, many units throughout the institute focus significant portions of their efforts in related research areas. Recently, within the Center for Research for Mothers and Children (CRMC), the NICHD created a new branch that will allow the NICHD to improve the safety and efficacy of pharmaceutical use by pregnant women and children. The new Obstetric and Pediatric Pharmacology Branch will coordinate research, clinical trials, and

drug development activities for obstetric and pediatric populations. It will also support, among other research networks, the newly formed Obstetric-Fetal Pharmacology Research Units (OPRU) Network. This network will support research on drug treatment during pregnancy. For instance, scientists will examine how drugs to treat diabetes in women are metabolized during pregnancy. The results from this initiative will also help physicians to prescribe drugs in a way that will be least likely to produce adverse effects for both a woman and her unborn baby. Also key in protecting women's health is the Pediatric, Adolescent and Maternal AIDS Branch, located in the CRMC. This branch supports research in the epidemiology, natural history, pathogenesis, transmission, and treatment of HIV infection and disease in women of childbearing age and in pregnant women, as well as in infants, children, adolescents, and families.

The Reproductive Sciences Branch, housed in the NICHD Center for Population Research (CPR), supports research to expand fundamental knowledge of the processes that underlie fertility and infertility in women, leading to the development of more effective strategies to diagnose, treat, and prevent conditions that compromise reproductive health. The Contraceptive and Reproductive Health Branch, also located in the CPR, not only develops new contraceptive methods, but also evaluates existing treatments and new therapies, such as microbicides, to determine how they affect a woman's overall health.

Another branch dedicating research to support women's health is the Pregnancy and Perinatology Branch (PPB), housed in the NICHD Center for Developmental Biology and Perinatal Medicine. The PPB supports research to ameliorate life-threatening conditions, including preeclampsia and preterm birth, saving the lives of women and their newborn children.

Reproductive Disorders

Fibroid Tumor Studies May Contribute to Developing New Non-surgical Treatments

NICHD researchers are beginning to unravel the mystery behind the origins of fibroids, the most common benign tumors of the uterus, and the leading cause of hysterectomy in the United States. Fibroids, also known as leiomyomas, can cause severe pain and infertility. This condition disproportionately affects African American women. In two recent studies of fibroid tumors, researchers discovered protein abnormalities that could help explain why the tumors grow and how they could be treated medically. In the study of fibroid tissues, researchers found that the tumors consist largely of abnormally tangled, loosely-packed "threads" (fibrils) of the protein, collagen. In the study of fibroid cells, researchers found an abnormally low production of dermatopontin, a protein involved in the manufacture of collagen. Lower levels of dermatopontin may contribute to abnormal collagen formation and, ultimately, to tumor development. These findings are major steps in understanding how fibroids form and may help in devising effective, non-surgical treatments for the condition.

The Basics of Healthy Pregnancies

A recent NICHD-supported study, *Discovering How an Embryo Attaches to the Uterus*, sheds new light on understanding the first biological steps needed to establish a successful pregnancy. About 6 days after fertilization, the embryo, or blastocyst, is shaped like a sphere. Its surface is composed of a layer of specialized cells called the trophoblast, which later gives rise to cells that form the fetus' part of the placenta (the placenta is made up of both maternal and fetal tissue). The trophoblast is coated with a protein known as L-selectin, while the wall of the uterus is coated with carbohydrate molecules. Researchers uncovered evidence that as the blastocyst travels along the uterine wall, the protein on its surface binds to the carbohydrates on the uterine wall, until the blastocyst gradually slows to a complete stop. Only after the binding takes place can the fetus implant itself in the uterine wall and a pregnancy begin. This finding may lead to insights into early pregnancy loss and the life-threatening complication of pregnancy known as preeclampsia, both of which may result from failures of the embryo to attach properly to the uterine wall.

Moreover, the finding may lead to a better understanding of some cases of endometriosis-associated infertility. Endometriosis is a disorder in which endometrial tissue—tissue

that normally lines the inside of the uterus—begins growing in other parts of the abdomen, such as the outside of the uterus, ovaries, or intestines. Endometriosis affects 10 to 15 percent of women of reproductive age, and is a major cause of infertility in women who have difficulty becoming pregnant. Another NICHD-supported research team found that women with infertility due to endometriosis have very low levels of the enzyme that makes the ligand for L-selectin. The ligand is a rubber-band like molecule that tethers L-selectin to the uterine wall. Researchers believe that without this enzyme, the embryo cannot attach to the uterine wall and a pregnancy cannot begin. The finding may lead to new therapies to treat women with endometriosis-related infertility.

Changes in Key Protein Levels May Cause Preeclampsia

Preeclampsia affects about 5 percent of all pregnancies and is a leading cause of maternal and fetal morbidity, disability, and death. A pregnant woman with preeclampsia has dangerously high blood pressure and the condition can progress to seizures and coma (eclampsia). The only cure for preeclampsia is delivery. Surviving infants are often premature and are likely to require intensive neonatal care. In an important step toward understanding the condition, researchers found earlier and more pronounced changes in the levels of several proteins in the blood samples of pregnant women who developed preeclampsia, compared to those from women experiencing normal pregnancies. Larger clinical trials are required to show if altered levels of these proteins can be used as a diagnostic marker for early detection and possible intervention.

New Standard for Labor and Delivery

More women are giving birth by cesarean section than in previous years, with more than one-fourth of all pregnant women, 26.1 percent, undergoing the procedure in 2002, up from 20.8 percent in 1997. Such factors as a woman's age and general health play a role in a doctor's decision to perform a cesarean section. A recent NICHD study, however, shows that the criteria on which doctors base their decision may no longer apply. Since the mid-1950s, physicians have based labor and delivery practices on the Friedman labor curve, a mathematical model depicting how the stages of labor should progress during normal delivery. However, on average, the characteristics of women giving birth today differ markedly from the population used to devise the Friedman labor curve. Compared to 50 years ago, obesity is far more prevalent, and women give birth later in life. Recently, researchers examined the pattern of labor progression in women in the 1990s giving birth for the first time. The researchers concluded that the Friedman criteria may be too stringent to determine when labor is proceeding much slower than expected. Moreover, the Friedman criteria may not apply to arrest disorders of labor, where the cervix does not dilate for 2 or more hours. In essence, researchers found that, for today's population of women, labor progressed more slowly than what was once identified as "normal" in the Friedman curve. These findings could have a profound impact on decisions about the need for cesarean delivery.

Improving Pregnancy Outcomes

Progesterone Injections Reduce Preterm Delivery

Preterm delivery (before 37 weeks of gestation) is the most important cause of infant mortality and morbidity in the United States. Furthermore, prematurity contributes substantially to racial/ethnic health disparities in infant mortality. It is also very costly. While preterm births account for 12 percent of births in the United States, new estimates show that hospital charges alone for premature/low birthweight babies reached $13.6 billion in 2001, accounting for one-half of hospital charges for all newborns. In addition, preterm babies are more likely to have long-term health problems. Women whose first baby was preterm are at high risk for subsequent preterm delivery. Until recently, most previously tested strategies to prevent preterm birth in such high-risk women failed to produce effective, reliable results. Early research using progesterone showed promise, but these studies were too small, and the methods and populations were too diverse, to yield conclusive results. Working collaboratively in the NICHD's Maternal-Fetal Medicine Units Network, researchers administered either pro-

gesterone (17P) or a placebo to a large group of women who had delivered a previous preterm infant. The 17P-treated women were 30 percent more likely than placebo-treated women to carry their babies to term, and their infants had lower rates of life-threatening complications. African American women benefited as much as white women from the experimental treatment. Furthermore, the researchers found no evidence that 17P caused birth defects or any other problem in the infants of treated mothers. Thus, 17P is a significant breakthrough that holds tremendous promise for reducing preterm birth and life-threatening medical complications in infants of high-risk women. This treatment may also begin to reduce the entrenched disparity in birth outcomes for African American infants.

Heavy Alcohol Drinking during Pregnancy Causes Persistent Nerve Damage in Infants that Escape Fetal Alcohol Syndrome

Heavy alcohol consumption during pregnancy can result in fetal alcohol syndrome (FAS). NICHD-supported researchers have now determined that heavy alcohol drinking during pregnancy can significantly damage the peripheral nervous system of infants that do not develop FAS. This is the first study to find peripheral neuropathy—a condition well-recognized in alcoholic adults—in children exposed to alcohol *in utero*. Neurological evaluations of these infants, at ages 6 and 12 months, showed damage both to the part of the nerve that carries signals to muscles and other tissue and to the part that insulates the nerve. These infants will continue to be monitored for emerging clinical symptoms that could not be measured in infancy. For instance, in adults, alcoholic peripheral neuropathy is associated with muscle weakness and impaired fine motor functioning.

Genes and Development

Rett Syndrome Protein Involved in Early Development

Rett syndrome (RTT) is a genetic disorder that gradually halts the healthy development of infant and toddler girls. Girls with RTT lose their ability to talk, to interact, and to move independently. They may also experience seizures and behavior disorders. Researchers have determined that RTT results from a defect in a particular gene, known as MeCP2, but were unsure of the gene's function. Recently, scientists gained an understanding of the gene's function by studying the aquatic frog, Xenopus. They found that a mutant form of the gene affects early embryonic development. Specifically, an excess number of cells that give rise to the brain were produced in Xenopus tadpoles that had the defective gene and they developed neurological problems similar to those seen in girls with RTT.

Study Identifies Novel Puberty Gene

The mechanisms that control sexual maturation heralding the onset of adult reproductive function remain a mystery. Puberty begins when a structure in the brain, called the hypothalamus, begins secreting a "master" reproductive hormone, known as gonadotropin releasing hormone (GnRH), which regulates fertility. NICHD-supported researchers are closer to understanding what dictates the onset of puberty after examining several members of a family who did not experience normal sexual maturation. The researchers found that all of these individuals, along with another, unrelated person, had abnormalities in a gene known as GPR54. The researchers subsequently developed an experimental mouse that lacked this gene and showed that these mice remain sexually immature. The problem lies with the inability of GnRH to be released from the hypothalamus. These findings may open the door to new ways of treating ovaries and testes that fail to mature in the absence of normal circulating levels of GnRH.

Parenting

Parents Can Influence Adolescents' Decisions on Whether to Start Smoking

Researchers have found that direct parental involvement with young adolescents, coupled with perceived parental disapproval of smoking, can influence young people not to start smoking as more and more of their peers do so. These findings are important because rates at which young adolescents start to smoke remain high compared to the rates for adults,

and because starting to smoke as an adolescent increases the likelihood that an individual will be dependent on smoking as an adult. Surveys of children at the beginning and end of sixth grade, and at the end of seventh grade, showed that children who thought that their parents generally "kept tabs" on them and would be upset if they knew that their child smoked, were less likely to smoke, while children who believed their parents to be less involved with them were more likely to start the habit.

Early Television Exposure Linked to Attention Problems in Children

Over the years, researchers amassed data from different studies that television viewing at an early age may be associated with decreased attention span in children. However, they had no data from long-term studies to support this observation until NICHD-funded researchers designed an observational study to test a hypothesis: that television exposure at 1 and 3 years of age was associated with attention span problems at age 7. The researchers analyzed data on more than 2,600 children who were part of the National Longitudinal Survey of Youth. Using advanced statistical methods, researchers found that the more television very young children watched, the more likely they were at age 7 to have attention problems. The researchers cautioned that since they used a special definition of such problems, their findings did not necessarily indicate that early television viewing is associated with clinically diagnosed attention-deficit hyperactivity disorder (ADHD) in the older children. Their findings suggest, however, that parents could reduce the risk of such problems by limiting the children's television viewing in the early years, when their brains are still rapidly developing.

Watching Television with a High Level of Sexual Content Is Associated with Earlier Teen Sexual Behavior

Researchers found that adolescents who watch television with high levels of sexual content are more likely to initiate sexual intercourse at an early age, compared with peers who view television programs with relatively little sexual content. The researchers acknowledge that it is nearly impossible to conclusively prove that the sexual content of television shows influences teen sexual behavior. It is conceivable, they wrote, that teens considering engaging in early sex are simply drawn to TV programming with sexual content. However, the researchers believe this latter possibility is highly unlikely. In the study, which followed almost 1,800 adolescents between the ages of 12 and 17, the researchers carefully controlled for factors known to influence early sexual activity, such as academic performance and family structure. In two rounds of interviews, a year apart, researchers found that youth in the 90th percentile of watching "television programs with a high level of sexual content" were twice as likely to initiate intercourse as those in the bottom 10 percent.

Family and Health

Children Not Harmed by Mothers Leaving Welfare and Going to Work

Major federal welfare reform legislation of 1996 created stringent work requirements for parents on welfare and raised concerns about potentially negative effects on children of welfare mothers entering the workplace. With NICHD support, and co-funding from the National Institute of Mental Health, five other Department of Health and Human Services agencies, and 14 private organizations, researchers are following a large sample of children in three cities (Boston, Chicago, and San Antonio) whose mothers are moving from welfare to work. The researchers are assessing cognitive achievement, problem behaviors, and psychological well being in preschool-age children and young adolescents. Findings from the first period of the study (1999 to 2001) do not show either significantly negative or positive effects in the preschoolers that could be attributed to a parent leaving welfare and entering the workforce. In fact, researchers reported some gains in adolescents' well being, which were associated with their mothers' entry into the workforce. These first findings should help to allay concerns about immediate adverse impacts on children of the welfare reform work requirements. Researchers will continue to follow the children to assess longer-term effects.

Earnings, Education, and Trust Help Form Stable Families

New findings in a major study indicate that unmarried parents are more likely to marry each other before their child's first birthday or form a lasting relationship, if the father has higher earnings and the mother has graduated from high school. By comparison, couples with less education and income were less likely to stay together to raise their child. The likelihood of forming a stable family is also higher if the mother and father each feel that the other supports the relationship with such behaviors as expressing encouragement and being willing to compromise. Factors that destabilize relationships between new parents include serious health or developmental problems of their child, lower earnings and less education, and a father who has other children with different mothers. These findings can help policy makers and community programs understand how they can better support fragile families so that parents can provide the stability that fosters the healthy development of their children.

Physical or Sexual Abuse Interferes with Family Formation

In a large study of family formation among low- and middle-income women, researchers found that women who were sexually or physically abused or witnessed abuse as children, or who were physically abused as adults, were less likely to be in lasting marriages or stable relationships, compared with women without a history of abuse. Among the women studied, the researchers found very high rates of abuse, with differing effects on relationships, depending on when the abuse occurred. For example, women who experienced abuse in childhood typically engaged in multiple, transitory, and often abusive relationships with men, while women with adult experience of abuse tended to avoid any relationships with men. The researchers suggested that the degree to which abuse interferes with family formation in the United States may be substantially underestimated and policies to foster stable homes should attempt directly to reduce the prevalence of abuse.

HIV/AIDS

Pregnancy and Progression of HIV Disease in Women

Although zidovudine (ZDV) sharply reduces a pregnant woman's chances of passing HIV on to her child, many are concerned that this benefit would come at the expense of the mother's own health. Specifically, could women in the early stages of HIV infection, who would not take anti-HIV drugs if they were not pregnant, speed the course of their own disease? Could such temporary exposure to ZDV allow the virus to develop resistance to the drug? NICHD-supported scientists recently found that when pregnant women in the earliest stages of HIV infection took ZDV temporarily, they did not experience accelerated HIV disease or excessive ZDV resistance for as long as 4 years after giving birth. Another study of women who took ZDV during a more advanced stage of HIV disease found a significant but very small increase in levels of the virus 18 months after the women gave birth. Because this small increase occurred both in women who stopped ZDV after delivery and those who continued it, scientists think that the slight elevation in HIV virus levels could stem, at least in part, from such pregnancy-related factors as changes in hormone levels or maternal blood volume following delivery. The findings from the two studies indicate that temporary use of ZDV during pregnancy and delivery neither accelerates HIV disease nor negatively affects a woman's response to later drug therapy. In another study, researchers found that a second pregnancy in an HIV-infected woman who has already had a child does not significantly affect the course of her disease. Together, these studies should help HIV-infected women and their physicians make more informed choices to protect the health of the mother as well as that of her child.

International Health

Preventing the Transmission of HIV from Mother to Child in Developing Countries

NICHD-supported researchers have shown that a combined treatment of short courses of both ZDV and nevirapine result in an 80 percent lower mother-to-child HIV transmission

(MTCT) rate than using ZDV alone. Furthermore, the transmission rates (less than 2 percent) were similar to those achieved with the more complex, expensive, three-drug regimens routinely prescribed in developed countries. This short, inexpensive two-drug regimen can be applied in developing countries to successfully prevent mother-to-child transmission of the HIV virus. Following the publication of this study, the Thailand Ministry of Public Health adopted this regimen as the standard for prevention of HIV MTCT, and the World Health Organization revised its recommendations and adopted this two-drug treatment program in developing countries for women who do not require antiretroviral therapy for their own health.

Multivitamins during Pregnancy and after Birth Delay Progression of HIV in Women

The NICHD examined alternative means to slow the progression of HIV in pregnant Tanzanian women who do not have access to anti-HIV drugs. High doses of the vitamins B, C, and E administered during pregnancy and for 5 years after birth were shown to impede the progression of HIV infection. Women on multivitamin therapy also had significantly higher levels of infection-fighting cells and lower levels of circulating HIV virus compared to women who did not receive the supplements. These findings indicate that the vitamins strengthened the women's immune systems and reduced the rate at which the HIV virus replicated itself. The low cost of a vitamin regimen could enable countries with limited resources to improve the health and increase the longevity of women living with HIV.

Initiatives

Request for Applications (RFAs)

RESEARCH NETWORKS AND TRAINING CENTERS

- **Women's Reproductive Health Research (WRHR) Career Development Programs**
  The NICHD and the NIH Office of Research on Women's Health (ORWH) continue to support the research career development of obstetrician-gynecologists who recently completed postgraduate clinical training. The program bridges clinical training with basic, translational, and clinical research relevant to women's reproductive health. (HD-03-020 and HD-04-014)

- **Specialized Cooperative Centers Program in Reproduction Research**
  This NICHD program is a national network of centers designed to foster multidisciplinary collaborations among basic and clinical scientists conducting reproduction research. The goal is to improve human reproductive health by speeding the transfer of basic science findings into clinical practice. (HD-04-003)

REPRODUCTIVE ORGAN DISORDERS

- **Leiomyomata Uteri: Basic Science and Translational Research**
  The NICHD, along with the ORWH, is supporting an effort to translate basic research findings on leiomyomata uteri (uterine fibroids) into new therapies for prevention, treatment, and cure of this common gynecologic disorder. (HD-03-005)

IMPROVING PREGNANCY OUTCOMES

- **Obstetric–Fetal Pharmacology Research Units (OPRU)**
  To better understand how treatment drugs affect pregnant women, the NICHD developed the OPRU. This network is designed to foster multidisciplinary collaborations among basic and clinical researchers to examine the effects of pharmacologic agents on normal and abnormal pregnancies. (HD-03-017)

- **Research into Mechanisms of Fetal Growth Restriction**
  Fetal growth restriction (FGR) results in significant perinatal complications, including fetal death, prematurity, complications during childbirth, and neonatal death. The goal is to examine the mechanisms of FGR and to gain a better understanding of the factors that regulate fetal growth during pregnancy. (HD-03-018)

- **Genomic and Proteomic Network for Premature Birth Research**
  To stimulate scientists to apply the latest state-of-the-art technologies to maternal and child health research, the NICHD plans to support research using genomic and proteomic technologies to accelerate the pace of premature birth research.

Researchers will use large-scale, high-output approaches to uncover factors that cause premature birth and will share the findings via a public web-based database. (HD-04-002)

Reducing Infant Mortality

- **Research on the Scope and Causes of Stillbirth in the United States**
  The NICHD established a national, multicenter network to better understand the extent and nature of stillbirths that occur without known medical causes. By developing essential baseline knowledge of stillbirths in the United States, researchers will be able to investigate unidentified causes of stillbirth, and to develop and improve ways to prevent or ameliorate the effects of these causes. (HD-02-025)

- **Prenatal Alcohol Exposure among High-risk Populations: Relationship to Sudden Infant Death Syndrome**
  The NICHD, in collaboration with the National Institute on Alcohol Abuse and Alcoholism, is supporting research to examine links between prenatal alcohol exposure and adverse pregnancy outcomes such as stillbirth, fetal alcohol syndrome, and sudden infant death syndrome. (HD-03-004)

Program Announcements (PAs)

Reproductive Health

- **Emerging Technologies for the Study of Reproductive Neuroendocrinology**
  Because certain reproductive diseases and disorders are the result of altered neuroendocrine function, the NICHD and the National Institute of Neurological Disorders and Stroke are encouraging researchers to examine the mechanisms by which the nervous system controls reproduction. (PA-03-079)

- **Reproductive Genetics and Epigenetics**
  This NICHD initiative encourages researchers to examine genetic and epigenetic mechanisms underlying sex determination, fertility, reproductive health, reproductive aging, and other topics in the area of reproductive genetics and epigenetics. (PA-04-049)

- **Endometrial Cell Function**
  The goal of this NICHD program is to enhance our understanding of the etiology and improve treatment and prevention of endometriosis. Research projects would involve examining how endometrial cell function is regulated at the cellular and molecular level. (PA-04-056)

International Health

- **Nutrition and the Development, Treatment, and Prevention of HIV Disease in Women, Infants, and Children**
  The NICHD is encouraging research on how nutrition affects health maintenance, HIV transmission, breastfeeding, and antiretroviral therapies. Researchers are also encouraged to advance the development of methods to assess nutrition and the development of functional biomarkers that indicate outcomes of the interrelationship between nutrition and HIV. (PA-03-163)

Microbicides

- **Integrated Preclinical/Clinical Program for Topical Microbicides**
  The NICHD and the National Institute of Allergy and Infectious Diseases are supporting multidisciplinary research to advance safe and novel topical microbicides and microbicide combination strategies that prevent transmission of HIV. (PAR-03-137)

- **Alternative Test Models for Assessing Genital Irritation of Microbicidal/Spermicidal Products**
  The NICHD encourages research to develop new assays and animal models that will more accurately and readily predict any irritation in women and men after using microbicidal/spermicidal products. (PAS-03-081)

Conferences and Workshops

Career Training

- **Women's Reproductive Health Research Scholars' Research Symposium**
  The Women's Reproductive Health Research (WRHR) Career Development Centers program was established in 1998 through the joint efforts of the NICHD and the

ORWH. This symposium, held March 31–April 1, 2003, brought together WRHR scholars and established investigators to address obstetric/gynecologic research from basic science to clinical applications. In addition, the meeting included sessions on career planning, effective grant writing, and study section review.

- **Women's Reproductive Health Research Program—Transition to Independence for Physician Scientists**
  The WRHR Career Development Centers program supports training for obstetrician-gynecologists in basic, translational, and clinical research in women's reproductive health. This October 27, 2003 workshop brought together leaders in the academic, professional, and scientific communities to examine future research career opportunities for WRHR-trained obstetrician-gynecologist physician-scientists to retain newly independent investigators in a research career path.

REPRODUCTIVE HEALTH

- **Specialized Cooperative Centers Program in Reproduction Research Meeting**
  The Specialized Cooperative Centers Program in Reproduction Research (SCCPRR) is a national multicenter program designed to promote multidisciplinary interactions between basic and clinical scientists. The May 13-14, 2003 meeting highlighted significant advances in research, technology, resource development, and bioinformatics. Participants included SCCPRR-supported researchers and collaborators supported by the National Cooperative Program for Infertility Research, the Reproductive Medicine Network, and the Contraceptive Development Centers.

- **Reproduction 2003 Meeting**
  This multidisciplinary meeting, held November 10, 2003, convened basic and clinical researchers to discuss cutting-edge research in the area of reproductive sciences. Participants discussed pioneering research studies projected to have tremendous impact on all aspects of biomedical research, clinical medicine and, ultimately, the health of the public.

- **International Conference on the Adrenal Cortex**
  This August 28-31, 2004 conference provided a forum for scientists to discuss recent discoveries in adrenal physiology, biochemistry, and molecular biology as they relate to hormone production. The meeting provided a framework for understanding the function of the adrenal cortex and its role in disease and overall health, including women's health.

PELVIC FLOOR DISORDERS

- **Basic Science and Translational Research in Female Pelvic Floor Disorders**
  This November 14-15, 2002 conference, co-sponsored by the NICHD and the ORWH, was held to stimulate collaborative basic and translational research and training on female pelvic floor disorders, including pelvic organ prolapse, and urinary and fecal incontinence. Women with these clinical conditions suffer an impaired quality of life and frequently require medical intervention.

- **Vulvodynia: Toward Understanding a Pain Syndrome**
  The goal of this NICHD workshop, held April 14-15, 2003, co-sponsored by the ORWH and the NIH Office of Rare Diseases, was to stimulate innovative basic research into furthering our understanding of the pathophysiology, pain mechanisms, and treatment strategies for vulvodynia. The workshop proceedings are available on the NICHD website (*www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=294*).

MAINTAINING HEALTHY PREGNANCIES

- **Pregnancy and Perinatology Branch Planning Workshop**
  The purpose of this December 5-6, 2002 workshop was for the Pregnancy and Perinatology Branch of the NICHD to review its accomplishments, undergo an extensive self-review of its programs, and identify areas that still require attention. The workshop outcomes were used to develop a strategic plan for the branch, which is available on the NICHD website (*www.nichd.nih.gov/publications/pubs/ppb/ppb_strategic_plan.htm*).

- **Implantation: Immune Responses**
  The purpose of this November 4-5, 2003 conference was to engage immunologists in a discussion of the importance of immunological mechanisms in establishing and maintaining pregnancy. The meeting participants discussed new approaches to understand the underlying mechanisms that make blastocyst implantation successful, and how disruptions to these mechanisms may result in infertility and pregnancy complications.

- **Long-term Followup of Prenatal Drug Exposure: Challenges and Opportunities**
  This workshop, co-sponsored by the NICHD and the National Institute on Drug Abuse, held March 23-24, 2004, brought together researchers to review state-of-the-art longitudinal studies on prenatal substance exposure and to outline a scientific agenda for future observational and intervention studies. The goal was to develop appropriate treatment and policies that benefit the vulnerable children affected by prenatal substance exposure.

Contraceptive Health

- **Depot Medroxy-progesterone Acetate (DMPA), Weight Gain, and Diabetes: Is There Any Relationship?**
  This November 20, 2003 workshop brought together clinicians from family planning clinics, epidemiologists, and endocrinologists to discuss possible relationships between DMPA (Depo-Provera), weight gain, and the development of type 2 diabetes.

Parenting

- **Father- and Mother-Child Relationships in Two- and Single-Parent Families**
  This August 23-27, 2004 conference brought together social scientists and public policy experts to discuss how mothers and fathers in single- and two-parent families, and how divorce affect child development, and to evaluate programs designed to help children to adjust to these situations. The meeting outcomes may help researchers and policymakers to develop improved intervention programs that foster relationships with both parents, even when the parents do not live together.

Family and Health

- **Workforce–Workplace Mismatch? Work, Family, Health, and Well-Being Conference**
  This conference, held June 16-18, 2003, launched a new initiative to test innovative approaches to improve child and family well-being by altering workplace policies and conditions. The goal of the meeting was to examine existing research from a variety of disciplines to assess the state of scientific knowledge and to develop new research directions.

- **Multicultural Studies of Social Development in Early Life**
  This June 15-16, 2004 workshop brought together researchers who are examining the role of acculturation on parenting, child development, and family life. The goal was to assess and evaluate how acculturation affects child health and human development.

HIV/AIDS

- **Workshop on Dual Protection: Preventing Disease and Protecting Fertility**
  This NICHD workshop, held January 9-10, 2003, brought together researchers supported under a program to examine strategies that couples used to protect themselves from unintended pregnancies and disease. The goal was to evaluate the research findings and propose future research directions.

- **Fertility Regulation and Systemic Hormones in HIV-infected and At-Risk Women**
  This conference, co-sponsored by the National Institute of Allergy and Infectious Diseases, the Food and Drug Administration, the Family Health International, the NIH Office of AIDS Research, and the Office of Research on Women's Health, was held January 13-14, 2003. As HIV-infected women are living longer and healthier lives with the advent of anti-retroviral therapy, participants discussed approaches to pregnancy prevention in HIV-infected and at-risk women.

- **Workshop on the Influence of Gender on HIV Risk**
  In 2001, the NICHD, the National Institute of Drug Abuse, and the National Institute of Nursing Research supported a research

program to examine how gender influences HIV risk. This March 14, 2003 workshop convened researchers supported under this program to discuss possible points of convergence and common measures among the different studies conducted in New York, Pennsylvania, North Carolina, South Africa, Malawi, and India.

Health Disparities among Special Populations of Women

- **Community Partnerships with African American Women Organizations to Reduce Sudden Infant Death Syndrome** The NICHD joined with the Alpha Kappa Alpha Sorority, Inc., the National Coalition of 100 Black Women, and the Women in the NAACP in a unique, year-long collaboration, Partnerships for Reducing the Risk of Sudden Infant Death Syndrome (SIDS) in African American Communities. The effort produced three regional summit meetings to raise SIDS awareness. The meetings provided the forum to instruct African American women and men, from all walks of life, so they could return to their communities and teach others simple ways to help reduce the risk of infant deaths due to SIDS. Meeting participants received outreach "kits," designed by the NICHD in collaboration with community-based organizations, that stressed the need to place infants on their backs to sleep. The summits also helped build an infrastructure—which includes women-serving, faith-based, community, and service organizations—that can now be used to disseminate an array of future health messages.

- **Modifiable Risk Factors Associated with the High Rate of Sudden Infant Death Syndrome among Northern Plains Indians** The SIDS rate among American Indians is the highest of any population group in the United States and, overall, is slightly more than double that of whites. The disparity is most acute in the Aberdeen Area of the Indian Health Service (AAIHS), where the SIDS rate is four times greater than that of the U.S. population. The NICHD collaborated with the AAIHS, the Centers for Disease Control and Prevention, and the Aberdeen Area Tribal Chairman's Health Board to study infant mortality among American Indians and to identify prenatal and postnatal modifiable risk factors that would reduce SIDS risk. The project, which utilized maternal interviews, standardized postmortem procedures, and medical chart reviews, revealed that even one visit by a public health nurse during pregnancy or soon after birth reduced the infant death rate due to SIDS by one-fifth compared to homes never visited. Furthermore, a mother's binge drinking (five or more drinks at a time) during the first trimester of pregnancy was associated with an eight-fold increased likelihood that her infant would die of SIDS. Finally, infants usually wearing two or more layers of clothing at night, not including the diaper, were six times more likely to die of SIDS. These findings highlight several key SIDS risk factors that can be targeted in future intervention programs for the American Indian population.

- **Encouraging Well-Child Care as a Strategy against Infant Mortality** Despite substantial progress, wide racial disparities in infant mortality remain in the United States. The gap is particularly wide in Washington, DC, where mortality rates for African American infants in 2000 were 16.1 infant deaths per 1,000 live births—more than double the national rate of 6.9 per 1,000 for all races. A randomized controlled trial, which was part of the NICHD-funded DC Initiative to Reduce Infant Mortality, tested a unique program of educational and supportive services for high-risk mothers and their infants. Nearly all of the mothers in the program were African American, had inadequate or no prenatal care, and had other risk factors including poverty and low educational levels. The program, Pride in Parenting (PIP), provided mothers with information about child health and development, and health and social service resources available to them. This information, along with training and social support for the mothers, was provided in home visits, parent-child developmental play groups, and parent support groups. Unlike similar programs that used nurses for home visits, the PIP

program achieved better acceptance by recruiting lay visitors from the mothers' own communities, and by training them extensively in child health and development before they began visiting the mothers. Another unique feature was that program staff neither arranged for nor accompanied mothers to health care and social service sites; instead, mothers were given information on available resources and coached in using services, but were solely responsible for ensuring that their children received the well-child care and immunizations. The program deliberately used lay home visitors to reduce the cultural barriers to health care that account, in part, for disparities in infant mortality and morbidity. Compared to mothers who used standard social services, mothers in the PIP program were more likely to: 1) begin well-child care earlier, 2) make more frequent well-child care visits, and 3) complete the scheduled immunizations for their infants. If successfully replicated, this model program could enable minority mothers to seek and use health care for themselves and their children more effectively.

Initiatives

Program Announcements (PAs)

- **Reducing Preterm and Low Birth Weight in Minority Families**
  The disparity in pregnancy outcomes among minorities is, by in large, preterm delivery and low birth weight. The NICHD, the National Institute of Nursing Research, and the National Institute of Dental and Craniofacial Research are promoting collaborative multidisciplinary biobehavioral research aimed at clarifying the mechanisms underlying disparities in pregnancy outcomes and at developing interventions to reduce such disparities. (PA-04-027)

- **Health Disparities among Minority and Underserved Women**
  The NICHD is participating in a joint initiative with the National Institute of Nursing Research, the National Institute on Drug Abuse, the National Institute of Diabetes and Digestive and Kidney Diseases, and the ORWH to encourage research aimed at reducing health disparities among racial/ethnic minority and underserved women. Research projects will focus on health promotion and health-risk reduction in minority and underserved women age 21 and older. (PA-04-153)

GENDER STUDIES

- **The Influence of Gender on HIV Risk**
  There is little research examining how different behaviors that are expected, both socially and culturally, of women and men affect HIV risk. In FY 2001, the NICHD and the National Institute of Mental Health published an RFA, The Influence of Gender on HIV Risk. The goal is to gain a better understanding of how gender influences the risk of HIV infection through sexual behaviors. Studies include research to identify modifiable factors of gender-based power; to examine how gender roles in young women and men develop, and how changes in attitudes influence their HIV risk; and to examine how gender roles may compromise the ability of women and men to communicate, to negotiate, and to engage in safer sexual behavior to prevent HIV transmission.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving craniofacial, oral, and dental health through research. As a central part of this mission, the NIDCR funds scientific research to prevent diseases and improve the quality of life for the millions of Americans who suffer from chronic diseases affecting the mouth and face. The NIDCR supports research in areas as diverse as understanding the oral infections that lead to dental decay, periodontal disease, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone disease; salivary gland dysfunction and disease; and connective tissue diseases and disorders. Because one quarter of all chronic pain is associated with the face and mouth, the NIDCR has

become a leader in the field of pain research. The NIDCR's commitment to the fundamental study of the body's hard tissues—teeth, cartilage and bone—has led to advances in biomaterials research and to the emerging field of tissue engineering and biomimetics, fields that use the body's own cellular and molecular processes to repair and regenerate tissues and organs. Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the NIDCR has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. Research advances that affect women, in particular, are to be found within many of the institute's broad research categories. This report highlights accomplishments and initiatives in the areas of chronic pain, temporomandibular disorders, osteoporosis and basic bone biology, cancers, autoimmune disease, human immunodeficiency virus (HIV) infection, health disparities, craniofacial anomalies and periodontal diseases, and systemic effects.

Accomplishments

Gender and Pain Research

Pain conditions, including those that primarily affect women, have been an active area of NIDCR-supported research for a number of years. Findings from studies indicate that gender-based differences in pain conditions are due, in part, to biological differences between women and men. For example, one study examined the role of sex hormones in the central processing of noxious signals coming from the temporomandibular joint (TMJ). The role of sex hormones was examined when the TMJ was under normal conditions and during chronic inflammation to establish if: 1) sex steroid replacement modifies medullar neuronal activity induced by stimulating the TMJ, 2) these hormones act through modification of glutamate receptor functioning, and 3) the MAP kinase signaling pathway contributed to neuronal activity induced by stimulating the TMJ. Preliminary findings showed that estrogen administration increased neuronal firing in superficial layers of the brain stem medullar complex after a noxious stimuli. In addition, C-fos immunochemistry showed an increase in neuronal activity in the same superficial layers under similar noxious stimulatory conditions. Furthermore, some preliminary results using inhibitors of NMDA-type glutamate receptors (AP5) showed that estrogen prevented the inhibition of AP5 receptors suggesting that NMDA receptors play a role in estrogen modifications of TMJ nociception. Another observation included that low doses of estrogen enhanced the release of glutamate, but not glycine, from the medullar complex after noxious treatment of the TMJ. In summary, estrogen may have an important role in modifying neuronal activity in specific laminae of the medullar dorsal horn induced by noxious treatments of the TMJ and can alter pro-inflammatory signals in these same regions.

A research component of a training grant seeks to identify the role of the female reproductive hormones relaxin and estrogen in the etiopathogenesis of TMJ disease in women. Recent findings indicated that relaxin increases the expression of the matrix metalloproteinases (MMPs) collagenase-1 and stromelysin-1 in TMJ disc fibrocartilaginous cells, but not in synoviocytes, suggesting a potential mechanism of action for this hormone in TMJ diseases.

Data from a series of studies have suggested that gender factors play a significant role in pain experienced. These gender role differences extend beyond personal self-ratings of pain characteristics and observed responses to experimentally induced pain, to differential judgments made by men and women observing pain in others. Results from a series of studies suggest that men and women rate common painful events differently and that their estimation of pain is influenced by socially learned gender roles and stereotypes. Females tend to rate pain and the distress associated with it as more severe and upsetting. However, experimental manipulations that modify gender-related expectations (instructions suggesting that "this is the type of task we have found that women can cope with better than men") were found to substantially reduce discrepancies in ratings between women and men. Investigators also found that women anchor their pain ratings ("worst imaginable pain" with childbirth or menstrual pain, while men use various injuries for their anchor in pain ratings).

Temporomandibular Muscle and Joint Disorders

Temporomandibular muscle and joint disorders (TMJDs) are important chronic pain conditions of particular interest to the NIDCR. NIDCR researchers are presently conducting basic and clinical research addressing the origin of the gender differences associated with TMJDs. For example, a study identified three genetic variants (haplotypes) of the gene encoding catecholamine-O-methyltransferase (COMT). The haplotypes are low pain sensitivity (LPS), average pain sensitivity (APS), and high pain sensitivity (HPS). These haplotypes encompass 96 percent of the human population and five combinations are strongly associated with variation in the sensitivity to pain. The presence of even a single LPS haplotype diminishes, by as much as 2.3 times, the risk of developing myogenous TMJD. The LPS haplotype produces much higher levels of COMT enzymatic activity when compared with the APS or HPS haplotypes.

Patients with TMJD have lower pain thresholds and greater sensitivity to pain. Some of the explanations include somatization and depression. Somatization is defined as the tendency to experience numerous physical symptoms for which no apparent organic cause can be determined. If a medical cause is present, somatization is said to occur when complaints about the bodily disturbance and dysfunction are in excess of the pathology. To address these issues, a study examined the relationship of somatization and depression with perception of and response to three different pain stimuli (palpations, pressure/pain thresholds, and ischemic pain) in TMJD patients after controlling for level of clinical pain. Findings showed that depression was associated with perceptual and behavioral responses to an ischemic pain task, but not to palpation pain perception. On the other hand, somatization was related to perceptual responses to palpation at clinically relevant anatomical areas (related to TMJD pain), but was not related to palpation of pain at non-clinically relevant sites of ischemic pain. Neither depression nor somatization was related to pressure pain thresholds, while depression was associated with ischemic pain threshold and tolerance times.

Other TMJD-related projects include: 1) building a three-dimensional interactive map of the human TMJ that would simulate the actual function of the joint *in vivo*, 2) improvement of a compact cone beam X-ray device for dental and maxillofacial imaging that could be helpful in diagnosing and monitoring TMJ disorders, and 3) the modification of the surface of titanium implants to add graded nanostructure for strength and a surface for the attachment and ingrowth of mesenchymal cells with the purpose of improving biocompatibility in TMJ implants.

The NIDCR recognizes that for the design and development of new implant materials it is necessary to understand the success and failure of TMJ implants when used in patients. Thus, the NIDCR supports a TMJ Implant Registry and Repository. Findings from this registry will provide insight into the strengths and weaknesses of TMJ implants' design, and enable improvements for future implant designs. Moreover, the availability of well-characterized biological materials and retrieved implant materials should help in basic and clinical studies focused on the pathobiology of TMJ diseases and disorders.

Osteoporosis and Basic Bone Biology

The study of bone and other mineralized tissues has been a mainstay of NIDCR-supported research since the institute's inception, not only because of its importance as it relates to teeth and jaws, but also as it relates to the growth and development of the entire craniofacial complex.

Bone is an active and dynamic tissue that continuously remodels throughout life. The process of bone remodeling consists of the cycle of bone formation and resorption performed respectively by osteoblasts and osteoclasts. An imbalance between bone formation and resorption will lead to a change in bone mass. In young or developing (< 20 years old) bone, bone formation dominates resorption, resulting in bone growth and development. In healthy adult (20 to 40 years old) bone, the processes of bone formation and resorption are delicately equilibrated, no increase or decrease in bone mass occurs. However, in aging bone, an imbalance of resorption over

formation often induces loss of bone mass, and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture.

Osteoporosis is considered to be a risk factor for tooth loss and edentulism in the elderly. In addition, estrogen deficiency may lead to bone demineralization and oral bone loss. NIDCR-supported scientists conducted a 3-year study of 135 postmenopausal women (with no evidence of moderate or severe periodontal disease) to determine whether the positive effects of hormone/estrogen replacement therapy (H/ERT) on post-cranial bone density are accompanied by similar positive effects on oral bone mass. The women received either daily oral conjugated estrogen (Premarin) alone; estrogen in combination with medroxyprogesterome (Prempo); or placebo. All participants also received calcium carbonate and cholecalciferol (vitamin D3) supplements and a yearly dental cleaning. At the end of the study, investigators assessed changes in alveolar crest height (using bite-wing radiographs) and alveolar bone density (using digital-subtraction radiography). Post-cranial bone density was measured in the lumbar spine and left femur by means of dual-energy x-ray absorptiometry. Results from the study indicate that H/ERT significantly increased alveolar bone mass, compared with placebo. However, an important and unexpected finding was that the placebo group who received only calcium and cholecalciferol supplements and a yearly dental cleaning experienced a statistically significant increase in alveolar bone density and a slight improvement in alveolar bone crest height.

The long-term effects of dietary calcium on bone development and growth have not been explored. The results in a study using rats given a low or high calcium diet at time of weaning show that young animals that receive low calcium increase their food intake and get fat. Animals with low calcium intake have less calcium in their bodies and may have more brittle or less dense bones. Thus, calcium intake could have an effect on the facial bones and dentition.

NIDCR intramural scientists found that the matrix gene biglycan is important for modulating the growth factors called bone morphogenic protein (BMP). It is important because animals that are unable to make biglycan develop osteopenia.

Osteoclast Activity

Initial findings from a study on the interaction between the neuroendocrine and skeletal systems suggest that serotonin, a well-established neurotransmitter, regulates the activities of osteoclasts, which are bone-reabsorbing cells. Deregulation of the serotoninergic system leads to depressive disorders and other psychological disturbances. In the United States, twice as many women as men are affected by a depressive disorder each year and serotoninergic disorders could be associated with changes in bone mass. Thus, commonly prescribed antidepressants that target the serotoninergic system (e.g., Prozac) may affect bone health and could be exacerbated in perimenopausal women. Another study is elucidating the function of the Cb1-b family of proteins in the regulation of osteoclasts activity. Using cell culture models, investigators reported that CB1 requires and recruits two other proteins, Pyk2 and Src, to form a molecular complex such that CB1 can trigger downstream signals to regulate osteoclasts. The identification of these proteins provides additional molecular targets that could be used to modulate osteoclast activities, and thereby provide opportunities for therapeutic intervention to control bone loss related to periodontal diseases and osteoporosis.

Cancer

Breast Cancer Cell Metastasis to Bone

Breast cancers metastasize preferentially to bone. The reason for this organ-specific metastasis is not clear, however, some researchers believe that the bone cell environment has growth factors that support the growth of these tumors. Intramural investigators found that breast tumor cells preferentially migrate and invade in vitro to extracts of bone over extracts of other tissues, such as liver, lung, or brain. Purified osteonectin specifically promoted the migration and invasion, *in vitro*, of several breast cancer cell lines, but was inactive with melanoma and fibrosarcoma cells. Furthermore, osteonectin increases protease activity in bone-metastasizing cancer cells, but not in melanoma, fibrosarcoma, or 3T3 cells. A new model was set up to measure metastasis to bone using green fluorescent-labeled breast cancer cells. Findings indicate that cells

transfected with osteonectin form fewer bone metastases, possibly due to a decrease in platelet aggregation. Understanding the factors that cause the cells to metastasize to bone may lead to new therapeutic approaches aimed at blocking metastatic disease.

Estrogen and Cancer

Estrogen is cardioprotective, and it has been shown that it is highly angiogenic. Females suffer vasculitic diseases, and one underlying mechanism for reduced ischemic complications is increased angiogenic molecules, including Il-6. In order to investigate further the mechanism for the effects of estrogen, intramural scientists used microarray technology to identify genes induced by estrogen and tamoxifen in endothelial cells. Several genes were found to be regulated, and this was further confirmed by RT-PCR. Heparanase is increased several-fold by estrogen and decreased by tamoxifen. Likewise, the soluble receptor, VEGFR-1, is downregulated in both endothelial and estrogen-sensitive breast cancer cells. This receptor is a negative regulator of angiogenesis. This is a novel mechanism that explains the "angiogenic switch" in estrogen-dependent breast cancer.

Autoimmune Disease

Autoimmune disorders disproportionately affect women and result in the unintended destruction of the body's own tissues. In the oral cavity the disorder is manifested in Sjögren's syndrome, which often involves dry mouth, a dysfunction of the salivary gland that results in a reduced or permanent cessation of saliva secretion. It is the second most common autoimmune disease in the United States estimated to affect 1 to 2 million people with a female:male ratio of nine to one. The inability to moisten foods and initiate the digestive process results in considerable morbidity and has a marked impact on affected individuals' quality of life.

Salivary Hypofunction (Dry Mouth)

Saliva is an important factor in the maintenance of oral health. Lack of adequate saliva causes severe impairments in oral heath. These include difficulty in swallowing, chewing, and speaking, as well as loss of enjoyment of food, increases in oral diseases such as dental caries, periodontal diseases, and other infections; nutritional deficiencies; and reduced quality of life. Many diseases and conditions can induce salivary gland hypofunction. For example, autoimmune diseases such as Sjögren's syndrome (SS) and rheumatoid arthritis often cause dry mouth. NIDCR intramural scientists are developing novel approaches to treat salivary gland dysfunction primarily using principles of gene therapy and tissue engineering.

Sjögren's syndrome is an autoimmune disease that predominantly affects women (90 percent of patients). Diagnosis of the disease remains difficult and lags disease onset by 6 to 10 years. To address this problem, NIDCR-supported researchers have developed an elegant new assay to detect auto antibodies in patient serum. The use of cell surface receptors, expressed in cultured cells, resulted in a sensitive cellular assay to detect auto antibodies associated with SS. Another group of NIDCR-supported scientists reported that specific subsets of SS patients could be identified based on specific antibody profiles. Together, these studies point to novel ways to identify and stratify patients with this autoimmune disease.

To determine the factors that contribute to the onset of SS, NIDCR-funded investigators studied the role of interferon gamma, a cytokine acting on both immune and epithelial cells. Deletion (knock-out) of the genes for interferon gamma or the interferon gamma receptor in the mouse model for SS, prevented the onset of disease symptoms. These results suggest that interferon gamma can play an important role in the development of SS. In the clinical research arena, NIDCR is supporting an International Sjögren's Disease Registry. This registry is actively recruiting patients.

NIDCR intramural scientists have completed a placebo-controlled, randomized clinical trial of a new biologic agent, Etanercept, which is useful in treating rheumatoid arthritis. Etanercept is an inhibitor of (and soluble receptor for) tumor necrosis factor (TNF)-α, a cytokine found in increased amounts in salivary and lacrimal glands of SS patients. Findings showed that while this drug is safe to use in SS patients, there was no evidence for any efficacy of Etanercept in treating the exocrine component of SS. Furthermore, the results suggest that either therapeutic concentrations of Etanercept were unable to reach salivary tissue after systemic administration, or that the role of TNF-α in

the pathogenesis of SS is less important than previously thought, or that a role for this cytokine is critical at an earlier time in the pathogenic mechanism.

Human Immunodeficiency Virus

The study of the oral manifestations of human immunodeficiency virus (HIV) infection has been of great interest to the NIDCR because oral lesions in HIV-infected individuals are frequent and varied, and are among the first symptoms of infection. The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic and the NIH launched a national cohort to study HIV infection among women in 1995. The study is known as the Women's Interagency HIV Study (WIHS) and the NIDCR has supported an oral health component in the WIHS protocol. The overall goal of the WIHS oral health component is to assess the course of oral conditions (caries, periodontal diseases, soft tissue lesions, etc.) over time in HIV-infected and -uninfected women. The introduction of highly active retroviral therapy (HAART) produced changes in the incidence of oral lesions in HIV-positive women. Reductions in the incidence of erythematous candidiasis and pseudomembranous candidiasis were observed. However, no changes in the incidence of hairy leukoplakia or oral warts were reported. Other findings from the WIHS include a higher prevalence of coronal caries among HIV-positive women than HIV-negative women at baseline and year 5 of the study. No significant difference in the prevalence of root caries was found and no relationship was found between HAART and an increased caries risk. The higher incidence of caries was associated with a decrease in stimulated and unstimulated saliva. In relation to periodontal diseases, progression of periodontal disease, as measured by pocket depth and loss of attachment, did not differ between HIV-positive and -negative women in this study.

Health Disparities among Special Populations of Women

The National Institute of Dental and Craniofacial Research's strategic plan includes as a goal the elimination of disparities in oral health status of vulnerable populations, including women of racial and ethnic minority backgrounds, the poor, and those with developmental or acquired disabilities. Several studies of the Centers for Research to Reduce Oral Health Disparities, which are jointly funded by the National Center for Minority Health and Health Disparities, focus on the important role that caregivers play with respect to early childhood caries (ECC). ECC is a particularly devastating form of dental caries that is prevalent in very young children from vulnerable populations. One randomized clinical trial tests approaches to disrupt the transmission of caries causing microbes from mother to child through the use of chlorhexidine rinse by the mother, prenatally, in combination with fluoride varnish use with the infants. Both the test and control groups of mothers receive oral disease prevention counseling. In another study, the primary caregivers of poor, African American children were interviewed about a broad array of psychosocial, behavioral, biological, and environmental factors that may be related to the oral health status of themselves and their children. The results of this first phase of the study were used to develop a tailored/targeted intervention. All caregivers in the study receive standardized oral disease prevention information via a video. The test group participates in motivational interviewing. The oral health status of both the caregivers and children are outcomes of the study.

Craniofacial Anomalies

Clefts of the lip and palate are common human birth defects of multifactorial etiology and approximately 70 percent are non-syndromic. NIDCR-supported researchers' reported that now they can predict whether some parents are more likely than others to have a second child with the "isolated" form of cleft lip and palate. Researchers indicate that their latest gene test applies to about 12 percent of isolated cleft lip and palate, or babies born with clefts only and no other birth defects. Previously, they reported that mutations in another gene account for about 2 percent of all cases of isolated clefts, meaning researchers in the field now can collectively screen for about 15 percent of isolated cleft lip and palate. In their latest paper, the scientists

report a so-called "haplotype" gene test, one of the first of its kind in medicine. A haplotype is the sum of several recurring variations in the usual DNA sequence of a species that are spaced out, like signposts, along a gene or chromosome. In this case, they found that distinct combinations of sequence variations in and around the gene IRF6 correlated with an increased chance that a child would be born with a cleft.

The Oral Cleft Prevention Program, being supported by the NIDCR, is part of the National Institute of Child Health and Human Development's Global Network for Women's and Children's Health Research program. The specific aim of this portion of the program is to reduce the recurrence of nonsyndromic cleft lip and/or palate in a high-risk group of women through supplementation with folic acid at preconception and throughout the first 3 months of pregnancy. The design is a case-control study followed by a randomized clinical trial. This two-phase study is being conducted in Argentina, Bolivia, Brazil, Chile, Columbia, Ecuador, and Venezuela. The case-control study started in January 2003. By September 2004, 339 infants were enrolled in the case control study with 105 determined eligible for the randomized trial. The maternal folate randomized trial started in January 2004 with 183 mothers enrolled by September 2004.

Periodontal and Systemic Disease

Several researchers have been studying the relationship between pregnancy outcomes and the mother's periodontal status. Examples are the Obstetrics and Periodontal Therapy (OPT) Study and the Maternal Oral Therapy to Reduce Obstetric Rick (MOTOR). The OPT Trial is a multicenter trial designed to determine if periodontal treatment in pregnant women with periodontitis increases the gestational age of at-risk preterm infants, thereby reducing the incidence of preterm birth. Eight hundred and sixteen pregnant women will be recruited into the trial. As of the end of FY 2004, 616 women had been recruited. Followup to determine birth outcome continues. The MOTOR trial is a multicenter clinical trial to determine the effects of periodontal therapy on the rate of preterm birth at gestational age less than 35 weeks as the primary outcome. Two treatment groups of 900 pregnant women each will be recruited and randomized to immediate treatment for their periodontitis or to treatment after delivery. Recruitment began in April 2004, and at the end of September 2004 a total of 23 women had been recruited.

Another NIDCR-funded project is trying to explain the link between periodontal diseases and preterm birth. *Fusobacterium nucleatum* is a gram-negative found in the oral cavity that is associated with periodontal disease and with preterm birth. *F. nucleatum* has been isolated from the amniotic fluid, placenta, and chorioamnionic membranes of women delivering prematurely. This study examined the possible mechanism underlying the link between these two diseases. *F. nucleatum* strains isolated from amniotic fluids and placentas along with those isolated from orally related sources invaded both epithelial and endothelial cells. The invasive ability may enable *F. nucleatum* to colonize and infect the pregnant uterus. Transient bacteremia caused by periodontal infection may facilitate bacterial transmission from the oral cavity to the uterus. To test this hypothesis, the investigators intravenously injected *F. nucleatum* into pregnant CF-1 mice. The injection resulted in premature delivery, stillbirths, and nonsustained live births. The bacterial infection was restricted inside the uterus, without spreading systemically. *F. nucleatum* was first detected in the blood vessels in murine placentas. Invasion of the endothelial cells lining the blood vessels was observed. The bacteria then crossed the endothelium, proliferated in surrounding tissues, and finally spread to the amniotic fluid. The pattern of infection paralleled that in humans. This study represents the first evidence that *F. nucleatum* may be transmitted hematogenously to the placenta and cause adverse pregnancy outcomes. The results strengthen the link between periodontal disease and preterm birth. This study also indicates that invasion may be an important virulence mechanism for *F. nucleatum* to infect the placenta.

Periodontal and Cardiovascular Diseases

Cardiovascular diseases (CVD) accounts for 57 percent of all deaths among American women. Several epidemiological studies are trying to determine the independent contribution of periodontal infections to the risk of arteriosclerosis and cardiovascular diseases. For examples, NIDCR is funding a prospective, population-based, multicenter study looking at the relationship between periodontal diseases, carotid atherosclerosis, and stroke. Participants in the study (711) received a comprehensive periodontal examination and an ultrasound of the carotid arteries. In addition, anthropometrics measures were obtained and participants were interviewed to assess sociodemographic characteristics, risk factors for stroke, and other medical conditions. Preliminary results suggest that the prevalence of carotid plaque increases with the number of missing teeth. Participants with periodontal disease have other risk factors for cardiovascular disease, such as smoking, poor diet, and low levels of physical activity. When considering those risks factors, researchers were able to observed a slight relationship between carotid plaque and tooth loss. The study will continue enrolling patients and future findings may provide more information on the potential but unproven link among periodontal disease, tooth loss, atherosclerosis, and stroke.

Periodontal Diseases and Diabetes

Periodontal infection may be an aggravating factor for diabetes in women. An epidemiological study, the Epidemiology of Diabetes Complication Study (EDC), is conducting an oral examination of participants with the purpose of evaluating the prevalence, incidence, and disease progression rates for tooth loss, periodontal diseases, dental caries, soft tissue pathologies, salivary dysfunction, and oral health behaviors of a type 1 diabetic cohort.

Initiatives

Request for Applications (RFAs)

- **Pathobiology of Temporomandibular Joint Disorders**
  The purpose of the initiative is to stimulate research aimed at delineating the mechanisms underlying the etiology and pathogenesis of orofacial structures associated with temporomandibular joint disorders (TMJDs). The RFA encourages a systems approach—from the gene, molecule, cell to tissue and organ—that will provide the basis to better understand TMJDs and will lead to the development of new insights into the treatment and management of these disorders. (RFA-DE-03-005)

- **Clinical Genetics of Craniofacial and Oral Disorders**
  The goal of this RFA is to promote research that will enhance clinical genetics studies of the genes and environmental factors that cause or modify susceptibility to craniofacial, oral, and dental disorders and diseases. (RFA-DE-04-004)

- **Mechanisms of Orofacial Pain: Anatomy, Genomics, and Proteomics**
  The purpose of this RFA is to encourage the use of genomic and proteomic approaches and imaging techniques to clarify the molecular events involved in: 1) acute orofacial pain, 2) the transition from unrelieved acute pain to chronic pain (i.e., neuroplasticity), 3) neuronal hyperexcitability as manifested by hyperalgesia and allodynia, and 4) chronic orofacial pain disorders of an inflammatory and neuropathic origin. This improved understanding could lead to new therapeutic interventions to effectively treat chronic pain conditions. (RFA-DE-05-004)

- **Prospective Studies on Craniofacial Pain and Dysfunction**
  The primary purpose of this RFA is to encourage experienced and established investigators in the area of epidemiology to submit proposals for a prospective cohort study that will identify the incidence of craniofacial pain and dysfunction and its risk factors. (RFA-DE-05-007)

Conferences and Workshops

- **International Workshop on Sjögren's Syndrome**
  The NIDCR co-sponsored an International Workshop on Sjögren's Syndrome to develop consensus outcome measures for clinical research on the disorder. The workshop, held in Bethesda, Maryland, on April 10-11, also was sponsored by the Sjögren's Syndrome Foundation, the National Eye Institute, the Office of Research on Women's Health, and private industry.

- **Third Scientific Meeting of the Temporomandibular Joint Association**
  The NIDCR co-sponsored the third scientific meeting of the TMJ Association on Advancing Diagnostic Approaches for TMJ Diseases and Disorders, held May 5-7 in Bethesda, Maryland. Participants included: physicians, dentists, federal health agency officials, medical scientists, bioengineers, medical imaging specialists, and TMJ patients interested in learning about progress in diagnosing and treating TMJ. Topics covered included: the diagnosis of TMJ diseases and disorders; new and emerging diagnostic technologies; the complexity of TMJ diseases and disorders; the limitations in predicting outcomes of specific treatments for individuals; and NIH recommendations for conservative treatments, with irreversible treatment selected as a last resort. The Office of Rare Diseases, the National Institute of Bioimaging and Bioengineering, and the Office of Research on Women's Health also co-sponsored the meeting.

- **Periodontal Host–Pathogen Conference**
  This symposium, held in September of 2004, included discussion on women's health. The main focus of the session was based on association between periodontal inflammation and at least two particular conditions of importance to women: adverse pregnancy outcomes and osteoporosis.

National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within the NIDDK's research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include: gestational diabetes; obesity (especially in racial and ethnic minority populations); coronary artery disease; cardiovascular and end-stage renal disease associated with diabetes; eating disorders; irritable bowel syndrome (IBS) and other functional gastrointestinal disorders; osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis (IC); urinary tract infections (UTIs); urinary incontinence; and lupus nephritis (the kidney disease of systemic lupus erythrematosus). Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other institutes and centers (ICs), such as the importance of hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease. The NIDDK supports research that directly addresses the important women's health questions cited above, both through basic research directed to understanding underlying disease processes, and through clinical research that translates this understanding into therapies and preventive interventions. In FY 2003 and 2004, the institute has made progress in the following areas important to women's health, which are highlighted in this report: prevention and treatment of diabetes and its complications; osteoporosis; thyroid disease; irritable bowel syndrome and other functional gastrointestinal disorders; liver disease research; obesity and nutrition; kidney disease; urinary tract infections; urinary incontinence; and interstitial cystitis. The Office of Research on Women's Health has worked with the NIDDK to foster research in many of these areas.

Accomplishments

Diabetes

An estimated 18.2 million Americans, including 9.3 million adult women, have diabetes. It is the leading cause of new-onset adult blindness, kidney failure, and non-traumatic lower extremity amputations. It also increases the risk of stoke, heart attack, and premature death. Women, in particular, are at a much greater risk of heart disease and stroke due to diabetes, and certain populations of older minority women are affected disproportionately by end-stage renal disease as a result of diabetes. Ninety to 95 percent of diabetes cases are type 2 diabetes. Women who are obese, women who have had gestational diabetes, and women who are members of racial/ethnic minorities in the United States are at significantly increased risk of developing type 2 diabetes. The NIDDK supports a large number of basic and clinical research programs for extramural and intramural scientists aimed at increasing knowledge and understanding of the genetics, basic biology, and metabolic defects of diabetes, while simultaneously developing and testing strategies to effectively prevent, treat, and manage diabetes and its complications, especially in populations at risk. The following highlights of NIDDK-supported diabetes research are particularly relevant to women's health.

Type 2 Diabetes

Type 2 diabetes patients are impaired in their ability to produce and to respond to insulin, a key metabolic hormone enabling cells to use glucose as fuel. The institute is supporting studies aimed at understanding the biologic basis for susceptibility to type 2 diabetes, including studies that may yield insights into disease etiology and markers in women. One research team recently reported results from a study in a large cohort of white women that suggest that elevated plasma levels of biomarkers of endothelial dysfunction may predict risk for type 2 diabetes. Insulin resistance is a sign of impending type 2 diabetes, and a number of research studies are examining the mechanisms by which estrogen may ameliorate insulin resistance; the ORWH has helped foster this research. A newly funded study will investigate endogenous sex-steroid hormones and fat cell-derived hormones and cytokines (adipokines), and the interrelationship of these biochemical factors with relevant genetic markers, in the development of type 2 diabetes in large cohorts of women and men. This study may uncover possible sexual dimorphism in risk for type 2 diabetes conferred by these factors, with potential implications for tailoring prevention or treatment strategies.

Preventing or Delaying Type 2 Diabetes

According to recent estimates, at least 41 million Americans have "pre-diabetes," a condition of impaired glucose metabolism that identifies them as high risk for developing type 2 diabetes. The NIDDK has established a study of the long-term efficacy of interventions that have been shown to reduce the risk of type 2 diabetes in overweight, pre-diabetic individuals. This study builds upon the results of the Diabetes Prevention Program (DPP) clinical trial, which was spearheaded by the NIDDK. This landmark trial demonstrated that type 2 diabetes could be delayed or prevented by lifestyle intervention (moderate exercise and weight loss) or by drug treatment (metformin) in high-risk adults, including racial and ethnic minorities who suffer disproportionately from the disease. Sixty-eight percent of the DPP study participants were women; the ORWH support for the DPP facilitated recruitment and retention of women with a history of gestational diabetes (13 percent of all female participants). The current Post-DPP Outcomes Study (DPPOS) study, which also has the ORWH support, is examining longer-term effects of the trial interventions on prevention of type 2 diabetes and its cardiovascular complications in DPP participants. It will also compare outcomes for women and men, and by age and ethnicity. Other associated health outcomes have been examined in the DPP participants; for example, emerging results indicate that the DPP lifestyle intervention had a positive effect on reducing prevalence of urinary incontinence in women. The long-term effects of the DPP interventions on UI and other associated health outcomes will be examined in the DP-POS, as well.

To promote the message of type 2 diabetes prevention to populations at risk, a new campaign has been launched through the National

Diabetes Education Program (NDEP). The NDEP is jointly sponsored by the NIDDK and the Centers for Disease Control and Prevention, and works in partnership with public and private groups on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis and, ultimately, to prevent the onset of diabetes. The NDEP's Small Steps. Big Rewards. Prevent Type 2 Diabetes education campaign is translating the results of the DPP into practical health information for the public. Within this campaign, the NDEP has recently launched the first national multicultural diabetes prevention campaign, with tailored campaign messages and materials for African Americans, Hispanic and Latino Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and older Americans.

Gestational Diabetes

Women can develop a reversible state of diabetes during pregnancy called gestational diabetes (GDM). GDM increases risk of pregnancy and birth complications for both mother and fetus. Moreover, women who have had GDM have a 20 to 50 percent chance of developing type 2 diabetes within the next 5 to10 years. GDM occurs more frequently among women who are African American, Hispanic and Latino American, or American Indian—minority groups already at disproportionately high risk for type 2 diabetes. A range of studies of GDM are being supported, from research to elucidate the underlying molecular mechanisms that trigger development of GDM during pregnancy (such as how pregnancy hormones may provoke insulin resistance) to studies to identify specific predictors or markers of type 2 diabetes development following GDM, particularly in high-risk Hispanic and Latino women. One investigator is currently building upon encouraging results obtained in an NIDDK-supported study of treatment strategies to reduce risk of type 2 diabetes development in Hispanic women with a history of GDM (the TRIPOD study) to test similar strategies in a non-federally supported study. A new study by a career trainee, co-supported by the ORWH, is examining the role of parity and inflammatory markers in the pathogenesis of GDM and type 2 diabetes in women. The National Diabetes Information Clearinghouse has recently issued a new, easy-to-read science-based publication on GDM. To inform women who have had GDM about its implications for them and for their children, and steps they can take to possibly reduce their risk of developing type 2 diabetes, the NDEP is planning a campaign tailored for this audience under the Small Steps. Big Rewards. Prevent Type 2 Diabetes campaign.

Preventing Type 2 Diabetes in Youth

An increasing number of girls, as well as boys, are being diagnosed with type 2 diabetes in youth and hence are diabetic during their childbearing years. The NIDDK intramural program studies among the Pima Indians of Arizona, who have among the highest rates of type 2 diabetes in the world, have shown that diabetes during pregnancy increases the later risk of diabetes and obesity in offspring in this population. Newly launched initiatives that are directly addressing the rise of type 2 diabetes among children and adolescents should help to break this vicious cycle. The NIDDK has launched Studies To Prevent or Treat Pediatric Type 2 Diabetes (STOPP-T2D), a clinical trial network. The group is conducting a multisite trial to seek the best treatment strategies. STOPP-T2D is also conducting pilot studies to assess the feasibility of a planned prevention trial designed to target food service and physical education changes in schools and to promote healthy habits, in hopes of preventing onset of type 2 diabetes.

Islet Transplantation

Islet transplantation is a possible treatment modality for type 1 diabetes. Pancreatic " islets" are the discrete cell clusters that contain the insulin-producing beta cells. The NIDDK maintains a strong research program in islet transplantation. Encouraging results in the past few years with American patients who have undergone an experimental islet transplantation procedure (the "Edmonton procedure"), using islets from human cadavers, has led to new efforts to enable this therapeutic approach to reach broader use. In 2004, the Collaborative Islet Transplantation Registry (CITR) released its first annual report to disseminate the knowledge gleaned from

86 transplantations performed in 12 medical centers in the United States and Canada; 66 percent of the islet recipients were women. The report (*www.citregistry.org*) analyzes many factors that can affect the outcome of this experimental procedure for people with severe or complicated type 1 diabetes. The NIDDK, in collaboration with the NIAID, has recently created a major new islet transplantation network to design and implement human islet transplantation studies in adult type 1 diabetes patients, focused on improving safety and long-term success, that may eventually result in improved treatment of the disease. Research objectives include increasing the supply of viable islets and reducing side effects of immunosuppressive medications necessary for transplant success.

Progress in Preventing Cardiovascular Complications of Diabetes

Cardiovascular disease (heart disease and hypertension) is the leading cause of death in patients with diabetes. The risk of death due to heart disease is increased two- to fourfold in all patients with diabetes, as compared to their age-matched non-diabetic counterparts. In women, the risk elevation is even greater—four- to sixfold. The Epidemiology of Diabetes Interventions and Complications (EDIC) is a long-term follow-up study to a clinical trial that demonstrated that intensive control of blood sugar levels reduces the risk of eye, nerve, and kidney complications in type 1 diabetes patients. Recent results from EDIC have shown that trial participants, who received intensive therapy, also had less thickening of the wall of the carotid artery over time—a measurement of atherosclerosis—than those who had received standard therapy during the trial. These significant results demonstrate the importance of strict blood glucose control on preventing damage to large blood vessels, with important implications for the prevention of cardiovascular complications.

Other clinical trials addressing cardiovascular disease and diabetes may prove especially beneficial for women. The Look AHEAD (Action for Health in Diabetes) clinical trial is under way to determine if lifestyle intervention can improve cardiovascular outcomes in obese patients with type 2 diabetes. Co-sponsors include the NHLBI, the NINR, the ORWH, the NCMHD, and the Centers for Disease Control and Prevention (CDC). The trial has enrolled 5,145 patients, 59.4 percent of whom are women and over one third are members of minority groups. This trial is comparing the effects of behavioral intervention to achieve and maintain long-term weight loss versus diabetes education alone on incidence of heart attack, stroke, and cardiovascular-related death in these patients. The total follow-up period will be 11.5 years. In addition to 15 extramural clinical centers across the United States, a Southwest American Indian Look AHEAD clinical center has been formed at the NIDDK Phoenix Epidemiology and Clinical Research Branch in Arizona. The NIDDK is also providing support to two major clinical trials led by the NHLBI, which are studying ways to improve the treatment and prevention of cardiovascular disease in type 2 diabetes patients, respectively, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI2D) trial and the Action to Control Cardiovascular Disease Risk in Diabetes (ACCORD) trial.

Genetic Markers of Diabetes and Susceptibility to Complications

Finding the genes that confer increased susceptibility to type 1 and type 2 diabetes will help researchers understand why some people develop diabetes and others do not. This is particularly important in light of the differing effects some genes may have on diabetes risk in different racial and ethnic populations. The NIDDK is supporting a number of major genetic linkage consortia to identify genes predisposing to type 1 and to type 2 diabetes and their complications, including diabetic kidney disease. Researchers supported by the NIDDK and others recently identified variants in a gene that may predispose individuals to type 2 diabetes. This gene encodes hepatocyte nuclear factor 4 alpha (HNF4A), a transcription factor that acts as a "master switch" regulating the expression of hundreds of other genes. HNF4A is active in many tissues, including the liver and pancreas. In the beta cells of the pancreas, HNF4 influences the secretion of insulin in response to glucose. These results are encouraging for researchers trying to identify genes that increase susceptibility to this disease. Because susceptibility to type 2 diabetes seems to involve a complex interplay of genetic factors,

other approaches to finding genes include "expression profiling" to identify genes whose expression is significantly altered in diabetes. These types of studies have recently implicated the altered expression of genes involved in mitochondrial metabolism. Another effort is an ongoing study of genetic factors that lead to both type 2 diabetes and obesity in the Pima Indian population of Phoenix, Arizona. Working closely with the Pima Tribal Council, the NIDDK is also studying the development of complications and the genes that predispose to diabetic kidney disease, which is highly prevalent among the Pimas.

Endocrinology

The NIDDK supports a substantial portfolio of basic and clinical research on or relevant to endocrine diseases and disorders. This research includes studies important to diseases disproportionately affecting women, such as thyroid diseases (including Graves disease, breast cancer, and osteoporosis). Many of these diseases evolve from disruption of normal patterns of signal transduction and control of gene expression by members of the nuclear receptor superfamily. Research on these diseases should benefit from the Nuclear Receptor Signaling Atlas (Nursa), a new consortium supported by the NIDDK, the NCI, and the NIA that is designed to develop, collate, and distribute information about nuclear receptor and co-regulator structure, function, and role in disease.

Osteoporosis

Osteoporosis has been reported in people of all ethnic backgrounds and the chances of developing osteoporosis are four times greater in women. According to the National Osteoporosis Foundation, approximately 10 million Americans have osteoporosis and 34 million more have low bone mass, placing them at increased risk for developing the disease. Osteoporosis is characterized by low bone mass and bone deterioration. The NIDDK supports extensive research on anabolic (growth-promoting) factors in bone, including parathyroid hormone (PTH), PTH-related protein (PTHrP), the Wnt family of nuclear receptors, and other bone-specific anabolic factors, such as the bone morphogenetic proteins. NIDDK-supported research on PTH (intramural and extramural) has led to the development of this hormone as a newly approved therapeutic agent for osteoporosis. Significant progress has also been made with PTHrP. In a recent clinical study of 16 postmenopausal women with osteoporosis, NIDDK-supported researchers found that PTHrP significantly increased bone formation over a 3-month period. Current studies are aimed at determining whether PTHrP may be better than PTH as a treatment option for osteoporosis.

Thyroid

Studies are ongoing on causes of autoimmune thyroid disease, which can affect 6 percent of women, leading to metabolic dysfunction. Abnormal thyroid function can also affect a woman's pregnancy. Thyroid hormone (TH) plays an important role in promoting normal fetal development during pregnancy. When maternal TH levels are too low (hypothyroidism) or too high (hyperthyroidism), the result could be increased fetal mortality or other fetal developmental problems. Hypothyroidism is treated with a synthetic form of TH, called levothyroxine. Pregnancy increases the requirement for TH, so the dose of levothyroxine in women with hypothyroidism is increased during pregnancy. In a recent study of 19 women who had hypothyroidism and desired pregnancy, researchers determined that the requirement for increased levothyroxine occurs very early in pregnancy—as early as the fifth week of gestation. Based on these novel observations, the researchers recommend that women with hypothyroidism be counseled before pregnancy to increase their levothyroxine dose immediately upon confirming pregnancy. Results from a second clinical study investigating the opposite situation suggest that high levels of TH could be damaging to the fetus and result in increased rates of miscarriage and low birth weights. Taken together, these studies emphasize the importance of maintaining normal TH levels during pregnancy and suggest adjustment of TH medicines earlier in pregnancy than is the current practice.

Digestive Diseases

Irritable Bowel Syndrome and Other Functional Gastrointestinal Disorders

Functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), are highly prevalent in the United States and more common in women than in men. The cause of these disorders is unknown, and they are associated with debilitating symptoms such as pain, gas, constipation, fecal incontinence, and/or diarrhea. An array of factors, including stress, emotions, diet, how the brain processes stimuli, and motility of the GI tract appear to contribute to many of these symptoms. A key goal for research is to understand the interplay of gut and brain pathways in these disorders, and to build upon this knowledge to design effective treatments. Progress has been accelerated through interdisciplinary research approaches. For example, symptoms of IBS—which causes recurrent bouts of pain and constipation or diarrhea—may be influenced by both abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. One research group has now found sex/gender-based differences in brain activity in IBS patients in response to anticipated or actual rectal stimuli—using magnetic resonance imaging they observed that women with IBS showed more activity in regions of the brain that process emotion, whereas men showed more activity in areas registering pelvic pain. This research was conducted by a group participating in an ORWH Specialized Center of Research for Women's Health, co-funded by the NIDDK, that is devoted to identifying sex-related differences in the visceral pain syndromes IBS and interstitial cystitis (a bladder disorder), which often occur in the same individual. Another research team has evaluated in women two interventions for treating psychological disabilities associated with moderate to severe IBS and other functional disorders specifically affecting the bowel (FBDs). One study compared cognitive behavior therapy (CBT) to education therapy, and a second study compared antidepressant treatment to placebo. They found that CBT was far more effective than education therapy. Antidepressant therapy was equally effective as CBT, but the drug had side effects that prevented some patients from staying on the medication. Subgroup analysis demonstrated that both treatments were more effective in patients with moderate symptoms than in those with severe symptoms. However, FBD symptoms of patients who also had depression were not improved with CBT or antidepressant therapy. These results suggest that patients with FBD can benefit from certain types of treatment strategies which can, in turn, improve their quality of life. Strengthening research in this area, the NIDDK has recently funded a GI Biopsychosocial (mind–body) Research Center, which will provide infrastructure core support for researchers at the institution who are studying functional GI and motility disorders.

Liver and Biliary Disease Research Enhancement

Liver and biliary disease is an important cause of morbidity and mortality in the United States. It disproportionately affects minority individuals and the economically disadvantaged. Women are disproportionately affected by certain liver diseases, such as primary biliary cirrhosis, drug-induced liver injury, and gallstones. The NIDDK has led two major efforts to strengthen biomedical research on liver diseases. First, it has established a Liver Disease Research Branch, led by an eminent hepatologist, within its Division of Digestive Diseases and Nutrition. Second, it has spearheaded a recently completed effort by a subcommittee of the Digestive Diseases Interagency Coordinating Committee to draw up a strategic Action Plan for Liver Disease Research. The plan, issued in December 2004, addresses the broad range of liver diseases and is meant to foster research that will help reduce the burden of liver disease in the United States. One of several major new liver research efforts launched by the NIDDK is the Drug-Induced Liver Injury Network. This multicenter clinical network will conduct studies of patients who have suffered severe liver injury because of both prescription and over-the-counter medications, nutritional supplements, alternative medicines and herbals, and develop standardized definitions and tools to identify and fully characterize cases of drug-induced liver injury. The overall goal is to obtain a clearer picture of the causes and epidemiology of drug-induced

liver injury, in order to help develop better ways to prevent, detect, and treat this problem.

Obesity and Nutrition

Obesity is increasing dramatically in the U.S. population and is now considered an epidemic. The problem is particularly severe for African American, Hispanic/Latino American, and American Indian women. Using the body mass index, a measure of weight relative to height, it is estimated that more than 65 percent of the U.S. adult population is overweight or obese, with nearly 31 percent meeting criteria for obesity. It is estimated that nearly half of non-Hispanic African American women and nearly 40 percent of Mexican American women are obese. Obese individuals are at increased risk for numerous life-threatening complications, including coronary heart disease, type 2 diabetes and its complications, stroke, and breast and colon cancer; it also causes morbidity by increasing the risks for osteoarthritis, gallstones, and urinary incontinence. The NIDDK supports basic and clinical research on multiple fronts—nutrition, physical activity, epidemiology, behavioral intervention, surgery, neuroendocrinology, and fat cell biology—to help understand the underpinnings of obesity, including basic biological differences that predispose to sex/gender differences in fat accumulation and deposition, and to determine how best to prevent overweight and effectively maintain a healthy weight. Ongoing special programs include the university-based core centers, the Clinical Nutrition Research Units (CNRU), and the Obesity/Nutrition Research Centers (ONRC). The NIDDK also supports the Weight-control Information Network (WIN). WIN provides health professionals and consumers with science-based information on obesity, weight control, and nutrition. A new brochure series, *Across the Lifespan*, offers brochures in English and Spanish for older adults, parents, pregnant women, and young- and middle-aged adults that explain healthy choices.

Obesity Research Enhancement

Trans-NIH efforts in obesity research have been strengthened by the work of the NIH Task Force on Obesity. This Task Force was established by the NIH Director and is co-chaired by the NIDDK and the NHLBI Directors; multiple ICs and offices, including the ORWH, are part of the Task Force. With input from the extramural community, the Task Force has developed and issued a strategic plan for NIH Obesity Research. This plan sets out short-, mid-, and long-term goals for research to understand the biologic and environmental factors contributing to obesity and to find effective ways to reduce/prevent obesity, particularly in at-risk populations. The plan seeks to maximize collaborations among the NIH components and to capitalize on their expertise and interest in developing obesity research initiatives, including initiatives with particular relevance for women. The NIDDK's efforts to meet the goals of the plan are being coordinated through its Office of Obesity Research, and complemented by work of the new NIDDK Clinical Obesity Research Panel (CORP). The NIDDK CORP, the successor to the National Task Force on Prevention and Treatment of Obesity, brings together external experts to advise the NIDDK Advisory Council on important clinical research needs related to obesity prevention and treatment.

Preventing Weight Gain in Pregnancy and Other Vulnerable Life Stages

Epidemiological studies have indicated that specific stages of life, including adolescence, marriage, post-pregnancy, and menopause, confer high risk for the development of obesity in susceptible individuals. Studies have also demonstrated a link between overweight during pregnancy and early weight gain in offspring. The NIDDK is supporting studies to devise effective strategies for obesity prevention in women and children (particularly in minority groups) addressing these vulnerabilities; the ORWH is helping to foster this research. Examples of progress include a recent report that a two-part intervention to prevent excess gestational weight gain and weight retention postpartum was successful in overweight and normal weight low-income women. These encouraging results came from a pilot study funded through an NIDDK-led initiative encouraging innovative approaches to obesity prevention, focusing on high-risk groups, and was co-funded by the ORWH. The report of an investigators' workshop convened by the NIDDK, which reviewed

progress on the pilot prevention strategies and identified barriers to prevention of weight gain in the target groups, has been published and can serve as a guide in strategy development.

Identifying Risk Factors for Obesity in Women

Ongoing studies are investigating biochemical, environmental, and behavioral factors that may predispose women to obesity and type 2 diabetes. In a large study of thousands of women, researchers recently found that sedentary behaviors—especially sitting while watching television—are predictive of significantly greater risk of obesity and type 2 diabetes. Those who, on average, watched more TV per day were at higher risk. In fact, each 2 hour per day increase in TV watching during the course of the study was associated with a 23 percent increase in risk for obesity and 14 percent increase in risk for developing type 2 diabetes. These findings can now be incorporated into strategies to prevent or reverse obesity in women. A new study is investigating metabolic differences between African American and Caucasian women that may affect risk for obesity and its complications; this study is co-supported by the ORWH.

Clinical Studies in Obesity Intervention Through Lifestyle Modification

Researchers continue to identify successful strategies to induce and maintain weight loss. Results of a controlled clinical trial have shown beneficial effects of exercise in young women and men who had sedentary lifestyles and were overweight or moderately obese. The exercise intervention consisted mainly of walking on treadmills, and the participants started with an initial 20 minutes and built up to 45 minutes per session, five sessions per week. Their goal was to burn a minimum of 400 calories per exercise session. Interestingly, the results differed between men and women: whereas men in the exercise program lost an average of 6 percent of their body weight, mostly fat, women in the program on average neither lost nor gained weight. In contrast, women in the control group gained extra weight by the end of the study period. The reasons for the differences between the results for men and women are as yet unclear, but these results suggest that diet modification to reduce energy intake, in addition to this level of exercise, would be necessary to achieve weight loss in women. The Look AHEAD clinical trial described previously will examine the long-term health effect of weight loss, through physical activity and decreased caloric intake, in 5,145 obese adults with type 2 diabetes. A newly established clinical trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE), will evaluate the impact of weight loss, resulting from a behavioral program, on urinary incontinence in overweight and obese women; this trial is being supported by the ORWH. The NIDDK is also pursuing research on long-term weight maintenance through a solicitation to encourage both basic and clinical studies in this area. With another new effort, the NIDDK is encouraging research on diet composition and energy balance to understand how different aspects of foods affect food intake, energy expenditure, and weight change—which could, in turn, inform efforts to develop effective lifestyle modifications to reduce overweight and obesity.

Assessing Surgical Approaches to Treat Obesity and Its Complications

Surgery to remove or enable loss of excess weight is one approach to treating overweight and obesity. A common surgical procedure utilized by persons who are overweight or obese is liposuction, which removes excess subcutaneous fat from specific areas of the body, including the abdomen, hips, and thighs. A recent study of abdominal liposuction in obese women with and without type 2 diabetes, however, revealed that this procedure to reduce fat mass did not reduce key obesity-related risk factors for obesity-related complications, such as type 2 diabetes and heart disease. This is likely due to the fact that, unlike other approaches to weight loss such as diet and exercise, liposuction does not remove visceral fat, nor does it affect energy balance. In contrast, bariatric surgery (gastric bypass surgery) to reduce stomach size and intestinal absorption of nutrients is a proven way to achieve and maintain weight loss in severely obese individuals, and improves most obesity-related conditions. However, these procedures carry a number of serious risks, and more evidence-based guidance is needed for patient evaluation, selection, and follow-up care. The

institute has established the Longitudinal Assessment of Bariatric Surgery (LABS) consortium to establish a large prospective database and conduct studies of the effects of bariatric surgery on the health and well-being of patients with extreme obesity and to identify patients most likely to benefit. Studies conducted by the consortium will also spur increased understanding of the pathogenesis of severe obesity and its complications. LABS will evaluate gender differences in the extent and durability of weight loss, co-morbidity improvement, and complications of bariatric surgery. The ORWH is providing support for LABS, which will enable the consortium to address issues relevant to women's health, such as how bariatric surgery affects menstrual and reproductive health, fertility, pregnancy, and urinary incontinence. LABS also will address whether some populations of women may be at higher risk for adverse surgical outcomes because of factors such as race/ethnicity, education, and socioeconomic status.

Biology of Overweight and Obesity

The NIDDK has spearheaded basic research on the neuroendocrine pathways and metabolic factors influencing energy balance, metabolism, and weight regulation. A current model for control of body energy balance includes an "appetite control center" in the brain's hypothalamus that integrates information about energy stores and needs in order to regulate appetite, eating, and physical activity. This information is provided by levels of hormones and other molecules, such as the fat hormone leptin, which acts on key neurons in the hypothalamus to suppress eating. In addition to uncovering possible opportunities for therapeutic interventions in the adult, scientists are building on the model to obtain a better understanding of how these circuits develop early in life and how amenable they are to adjustment later on (i.e., how "plastic" they are.) For example, recent studies in rodent models have now shown that leptin doesn't just transmit information to the brain about fat stores, but is also fundamentally involved in developing the neural circuits in the brain that control feeding. Research in this area will be strengthened by a planned initiative to solicit studies of the effects of the intrauterine environment, particularly effects of maternal metabolic status, on the development of energy balance pathways in offspring.

Ancillary Studies to Obesity Clinical Trials

To capitalize on major ongoing NIH research investments in obesity, the NIDDK has partnered with the NIA and the NCCAM in launching an initiative soliciting ancillary studies to several existing obesity-related clinical trials and networks, including Look AHEAD, the DPPOS, LABS, and PRIDE. Acceptable studies may include investigation of the genetic and environmental factors underlying obesity, of the pathogenesis of obesity and associated co-morbidities, of surrogate markers or biomarkers for obesity-related disease and therapeutic effects of interventions, and of new technologies for measurement of diet, physical activity, and energy balance.

Kidney Disease and End-stage Renal Disease

An estimated 8 million Americans have chronic kidney disease, of whom more than 400,000 have end-stage renal disease (ESRD), with over 300,000 requiring dialysis to live. Diabetes and high blood pressure are the leading causes of kidney failure, and cardiovascular disease is a leading cause of death for ESRD patients. Prevalence of irreversible kidney failure is much higher in ethnic and racial minorities within the United States, and older American Indian and African American women are affected disproportionately by kidney failure due to diabetes. Women are also differentially affected by certain kidney diseases, including kidney disease due to lupus and preeclampsia. A major new educational outreach effort, the National Kidney Disease Education Program (NKDEP), is designed to raise awareness among patients and physicians about the problem of kidney disease and steps that should be taken to treat chronic kidney disease and prevent kidney failure—particularly in populations at risk.

Lupus Nephritis

Kidney disease represents one of the common and often serious manifestations of systemic lupus erythematosus (SLE), an inflammatory connective tissue disease that affects different

organ systems in varying combinations. The majority of patients afflicted with SLE are young women of childbearing age. Most people with SLE have some degree of renal disease, and many have kidney failure. The importance of renal involvement as a major cause of both morbidity and mortality of SLE has been well established. Thus, an understanding of the causal mechanisms and treatment is of significant interest to the NIDDK. Ongoing research seeks to develop better understanding of the immunologic events leading to immune deposit formation in the glomerulus of the kidneys. Results of ongoing studies should identify disease-relevant glomerular antigens for pathogenic lupus autoantibodies, provide insights into overall pathogenic relevance of autoantibody-glomerular cell surface interactions in lupus nephritis, and identify possible susceptibility genes for this disease. Moreover, basic research is elucidating mechanisms that may be involved in antibody complex clearance from the glomeruli, providing further insights into pathology of kidney diseases in which antibody deposition is a key factor.

Chronic Kidney Disease and Cardiovascular Health

ESRD patients are known to have very high rates of cardiovascular disease (CVD) but, until recently, it was unknown to what degree less serious chronic kidney disease predisposes patients to develop CVD. The Modification of Diet in Renal Disease clinical trial provided strong evidence that kidney function can be reliably estimated by measuring the amount of a compound called creatinine in a patient's blood, and performing a calculation that also includes variables such as the person's size and sex. Now, researchers have built upon that finding by examining the results of creatinine tests from more than one million patients to assess kidney health and look for correlations with cardiovascular outcomes, such as heart attacks. The researchers found a very clear pattern: the poorer a patient's kidney function, the more likely he or she was to develop CVD. Armed with the knowledge that kidney health is a predictor of CVD, health care providers can now determine that some of their patients are at risk, and may be more likely to benefit from earlier, more aggressive cardiovascular treatment than might otherwise have been prescribed. A study currently under way, the Chronic Renal Insufficiency Cohort study, is a multicenter, longitudinal cohort study seeking to identify the factors that contribute to the decline in kidney function and the development of cardiovascular disease in people with chronic kidney disease.

Preeclampsia

Preeclampsia affects approximately 3 to 4 percent of pregnancies and is the leading cause of maternal and fetal death in the United States. Mothers with preeclampsia develop hypertension, proteinuria, and edema—all resulting from widespread endothelial dysfunction. Abnormal endothelial growth in the glomeruli is the typical kidney lesion of preeclampsia. Although the symptoms are known, the cause of preeclampsia has remained elusive. Researchers recently found that a soluble protein, sFlt1, is strongly associated with the symptoms and lesions of preeclampsia. They observed significantly higher serum levels of sFlt1 in preeclamptic pregnant women than in normotensive pregnant women. In contrast, serum levels of free VEGF and free PlGF—two proangiogenic factors known to be inhibited by sFlt1—were significantly lower in preeclamptic mothers. *In vitro* experiments suggested that excess levels of sFlt1 could indeed be interfering with VEGF and PlGF to disrupt angiogenesis and to induce hypertension. Most significantly, the team was able to reproduce human preeclampsia symptoms and lesions in a rat model by the addition of the sFlt1 protein. Independently, a study in rodents has shown that targeted reductions in VEGF production by cells within the glomeruli cause kidney lesions similar to those seen in preeclampsia. The results of these studies are encouraging, for if exposure to excess sFlt1 is responsible for some or all preeclampsia symptoms in pregnant women, then treatments to overcome its activity may ameliorate symptoms. Sflt1 may also turn out to be a useful biomarker for the development of preeclampsia.

Sex and Gender Differences in Kidney Function

Sex- and gender-based differences in kidney function in health and disease can affect vulnerability to renal dysfunction. The NIDDK is supporting studies of these differences,

including a new basic study of the effect of estrogen on the transport of xenobiotics in the kidney, and a new epidemiological study to examine risk factors for renal function decline among 5,000 women in the Nurses' Health Study I and the Nurses' Health Study II. The latter project includes study of threshold levels of safe cumulative dose of individual classes of analgesics, and will provide the opportunity to define the predictors, such as analgesic use, of renal function change in women. These studies are co-supported by the ORWH.

Women's Urologic Health

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract are a leading cause of urinary incontinence, pelvic pain, and kidney failure, and they often contribute to poor quality of life. Women are disproportionately affected by urological diseases, especially urinary incontinence, urinary tract infections, and interstitial cystitis. Through its basic, clinical, and epidemiological research programs in urology, the NIDDK is continuing efforts to improve interventions and treatments for these diseases, and to better understand their underlying causes. The institute is seeking to strengthen its basic and clinical women's urologic health research portfolios through its current recruitment of an individual with appropriate expertise to foster scientific programs in these areas and to lead development of a science-based women's urologic health outreach initiative. The NIDDK is also supporting the Urologic Diseases in America (UDA) project. This important project is closing many of the former gaps in knowledge about the prevalence, incidence, treatment, and economic impact of urologic disease in the United States. The UDA recently released an interim compendium that included urinary incontinence, urinary tract infection, and sexually transmitted diseases. The full report will include urethral diseases and interstitial cystitis.

Recurrent Urinary Tract Infections—Insights into Causes and Treatments

Urinary tract infections (UTIs) are among the most common infectious diseases acquired by humans; in fact, only respiratory infections occur more often. Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract. UTIs caused by the bacterium *Escherichia coli* (*E. coli*, normally found in the colon) accounted for 7.9 million doctor visits by women in 2000, and many women suffer from frequent infections. NIDDK-supported researchers have made several important discoveries about UTIs. For example, researchers have recently shown, in a comprehensive set of studies, that uropathogenic *E. coli* can invade, multiply, and persist within mouse bladder cells. Their results suggest that at least some UTI recurrences may be due to resurgences of a single infection rather than fresh infections, and are being followed up with studies of clinical samples. This research team is participating in an ORWH Specialized Center of Research co-supported by the NIDDK, that is supporting three major, interlocking projects devoted to elucidating the molecular and epidemiologic bases of acute and recurrent UTIs. A prospective clinical study of women with recurrent UTIs is ongoing. Results of this research may lead to new means of evaluating UTIs and new and better ways to treat infection.

Interstitial Cystitis—Clinical Trials of Treatments

Interstitial cystitis (IC), one of the chronic pelvic pain disorders, is a condition of unknown cause resulting in recurring discomfort or pain in the bladder and the surrounding pelvic region. As many as 847,000 Americans may have IC, however, 94 percent are thought to be women. NIDDK-supported basic and clinical research studies are focused on elucidating the cause(s) of IC and on improving treatment and interventions. Current strategies for IC therapy are aimed at alleviating symptoms of pain and frequent urination and range from oral medications to surgery; however, these treatments are often invasive and not effective in all patients. Results from the first NIDDK-supported clinical trial of treatments for IC have been reported. The study, conducted by the IC Clinical Trials Group, compared two oral medications, one already FDA-approved for IC, as well as a second drug for possible use either alone or in combination to bring more potent relief of IC symptoms. Unfortunately, neither drug alone or in combination produced a significant benefit; however, the trial has provided important information for future research on therapies. A second 5-year IC clinical trials

group, the IC Clinical Research Network, has been established with enhanced opportunities to develop ancillary studies in conjunction with the clinical trials. Trial protocols are currently under development. Biomarkers for IC, which could aid diagnosis and the study of treatment efficacy, will be sought and studied in these ancillary studies. In particular, a promising biomarker of IC, APF, is being studied.

Advancing Basic Understanding of Interstitial Cystitis

While clinical trials proceed to attempt to improve treatments for IC, a better understanding of the basic biology of IC is also desired to help uncover its cause(s). Through a recent research solicitation, the NIDDK is supporting new studies of basic biology of IC, including genetic studies. These studies will employ a variety of research approaches to improve our understanding of the IC bladder and the molecular mechanisms underlying the cause(s) and symptoms of IC. For example, recent studies have described the effects of APF exposure on molecular pathways controlling cellular growth in bladder epithelial cells, which may provide insights into the pathogenesis of IC. Other studies are focusing on how sensory neurons perceive stimuli, neurogenic inflammation, and signaling molecules released by the bladder epithelium. The NIDDK also added to its IC portfolio through a research solicitation for epidemiological studies to investigate prevalence. A new epidemiological study to identify cases of IC and painful bladder syndrome has been launched; the ORWH is providing support for this study.

Raising Awareness of Interstitial Cystitis

Diagnosis of IC is currently a symptom-based diagnosis of exclusion, and IC patients have reported significant delays between onset of symptoms and diagnosis (5 to 7 years). To address gaps in knowledge among the public and health care providers, the NIDDK has initiated a new Interstitial Cystitis Awareness Campaign that will reach out to three specific audiences: urologists, the public, and family care practitioners. Outreach materials for this campaign include information on therapeutic options for IC patients. The National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC) is the primary distribution channel for campaign materials.

Urinary Incontinence

In community-dwelling adults, urinary incontinence affects an estimated 35 percent of women 65 years or older and 10 percent of women younger than 65 years. Urinary incontinence, which affects mostly women, is a problem often associated with pregnancy, childbirth, and aging. Research is ongoing, but treatment options for urinary incontinence are currently limited to physical therapy to improve muscle tone and bladder control, and to surgical procedures. The multicenter Urinary Incontinence Treatment Network (UITN) was established to conduct clinical trials of treatment strategies for urinary incontinence. The UITN has already begun a randomized, controlled clinical trial comparing two surgical treatments for stress and mixed incontinence in women. The UITN is currently enrolling patients for a second trial, which will focus on treating women with pure or predominantly urge incontinence. This trial, the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) trial, will compare effects of two interventions, drug therapy alone, and combination drug therapy and behavioral treatment, on the frequency of urinary incontinence and success in withdrawing patients from drug therapy. The UITN is also collecting data on body weight and diabetes, which could as a resource for ancillary studies to investigate the association of urinary incontinence with obesity and diabetes. The UITN is co-sponsored by the NICHD and has also received support from the ORWH. As previously mentioned, the Program to Reduce Incontinence by Diet and Exercise (PRIDE) clinical study has been initiated to evaluate the impact of weight loss, resulting from a behavioral program, on urinary incontinence in overweight and obese women.

Initiatives

Program Announcements (PAs)

- **Pilot and Feasibility Program in Urology**
  This PA is co-sponsored by the NIDDK, the NCI, and the NICHD. (PA-04-146)

- **School-based Interventions to Prevent Obesity**
  This PA is co-sponsored by the NIDDK, the NICHD, the NHLBI, the NINR, the OBSSR, and the NCI. (PA-04-145)

- **Exploratory Grant Program in Diabetes Endocrinology and Metabolism** (PA-04-137)
- **Understanding and Promoting Health Literacy (R01)**
  This PAR is co-sponsored by the AHRQ, the NIDDK, the OBSSR, the NCI, the NIA, the NHLBI, the NIBIB, the NICHD, the NIDCD, the NIDCR, the NIDA, the NIEHS, the NIMH, and the NLM. (PAR-04-116)
- **Understanding and Promoting Health Literacy (R03)**
  This PAR is co-sponsored by the AHRQ, the NIDDK, the OBSSR, the NCI, the NIA, the NIBIB, the NICHD, the NIDCR, the NIDA, the NIEHS, the NIMH, and the NLM. (PAR-04-117)
- **Innovative and Exploratory Research in Digestive Diseases and Nutrition**
  This PA is co-sponsored by the NIDDK, the NCI, and the ODS. (PA-04-108)
- **Long-term Weight Maintenance: Basic and Clinical Studies**
  This PA is co-sponsored by the NIA, the NINR, and the ODS. (PA-04-092)
- **Ancillary Studies to Major Ongoing NIDDK Clinical Research Studies** (PAR-04-078)
- **Health Disparities in NIDDK Diseases** (PA-04-074)
- **Research Grants for Clinical Studies of Kidney Diseases** (PAR-04-065)
- **Diet Composition and Energy Balance**
  This PA is co-sponsored by the NIDDK, the NCI, the NCCAM, the NHLBI, the NIA, the NIAAA, the NICHD, the NINDS, and the ODS. (PA-04-033)
- **Insulin Signaling and Receptor Cross-Talk**
  This PA is co-sponsored by the NIDDK and the NIA. (PA-03-156)
- **Basic Research in the Bladder and Lower Urinary Tract**
  This PA is co-sponsored by the NIA and the ORWH. (PA-03-136)
- **Ancillary Studies of Kidney Disease Accessing Information from Clinical Trials, Epidemiological Studies, and Databases** (PA-03-091)
- **Calcium Oxalate Stone Diseases** (PA-03-065)
- **Planning Grants for Translational Research for the Prevention and Control of Diabetes**
  This PAR is co-sponsored by the NIDDK, the NEI, and the CDC Division of Diabetes Translation. (PAR-03-060)
- **Endoscopic Clinical Research in Pancreatic and Biliary Diseases**
  This PAR is co-sponsored by the NIDDK and the NCI. (PAR-03-033)
- **Bone Anabolic Hormones, their Receptors and Signal Transduction Pathways**
  This PA is co-sponsored by the NIDDK, the NIA, the NCI, the NIAMS, and the NIDCR. (PA-03-008)
- **Age-related Changes in Tissue Function: Underlying Biological Mechanisms**
  This PA is co-sponsored by the NIDDK, the NIA, the NCI, the NIDCD, and the NIDCR. (PA-03-147)
- **Integrative and Collaborative Approaches to Research**
  This PA is co-sponsored by the NIDDK and the NIGMS. (PA-03-127)
- **Research on Microbial Biofilms**
  This PA is co-sponsored by the NIDCR, the NIAID, the NIDCD, the NIAMS, the NIGMS, the NHLBI, the NIDDK, and the NIBIB. (PA-03-047)
- **Novel Genetic Methods to Map Functional Neuronal Circuits and Synaptic Change**
  This PAR is co-sponsored by the NIDA, the NIA, the NIAAA, the NIDCD, the NIDDK, the NEI, the NIMH, the NINDS, and the NICHD. (PAR-03-007)

Request for Applications (RFAs)

- **Building Interdisciplinary Research Careers in Women's Health** (RFA-OD-05-002)

- **Prevention and Treatment of Childhood Obesity in Primary Care Settings** (RFA-HD-04-020)
- **Clinical Nutrition Research Unit Core Centers** (RFA-DK-04-016)
- **Silvio O. Conte Digestive Diseases Research Core Centers** (RFA-DK-04-014)
- **Partnerships between Basic and Clinical Researchers in Obesity** (RFA-DK-04-010)
- **Diabetes Endocrinology Research Centers** (RFA-DK-04-007)
- **Clinical Islet Transplantation: Clinical Centers** (RFA-DK-04-005)
- **Clinical Islet Transplantation: Data Coordinating Center** (RFA-DK-04-004)
- **Ancillary Studies to Obesity-related Clinical Trials** (RFA-DK-03-022)
- **Pilot and Feasibility Program in Human Islet Biology** (RFA-DK-03-021)
- **Bench to Bedside Research on Type 1 Diabetes and Its Complications** (RFA-DK-03-019)
- **Genetic Studies of Obesity-related Traits in Model Organisms** (RFA-DK-03-018)
- **Silvio O. Conte Digestive Diseases Research Core Centers** (RFA-DK-03-016)
- **Innovative Partnerships in Type 1 Diabetes Research** (RFA-DK-03-015)
- **Innovative Grants on Immune Tolerance** (RFA-AI-03-010)
- **Cranberry: Urinary Tract Infection and Other Conditions** (RFA-AT-03-004)
- **Clinical Research Education and Career Development (CRECD) in Minority Institutions** (RFA-RR-03-007)
- **Maintenance of Long-term Behavioral Change** (RFA-OB-03-003)
- **Mind–Body Interactions and Health: Exploratory/Developmental Research Program (R21)** (RFA-OB-03-005)
- **Mind–Body Interactions and Health: Research Infrastructure Program (R24)** (RFA-OB-03-004)
- **Autoimmunity Centers of Excellence** (RFA-AI-02-006)
- **Hepatitis C: Natural History, Pathogenesis, Therapy, and Prevention** (RFA-DK-03-011)
- **Frequent Hemodialysis Clinical Trials** (RFA-DK-03-005)
- **Basic Research in Interstitial Cystitis** (RFA-DK-03-010)
- **Bariatric Surgery Clinical Research Consortium** (RFA-DK-03-006)
- **Interstitial Cystitis Clinical Research Network (ICCRN)** (RFA-DK-03-003)
- **Bench-to-Bedside Research on Type 1 Diabetes and its Complications** (RFA-DK-03-001)

Conferences and Workshops

- **NIDDK New Investigators Workshop** September 27-28, 2004
- **Workshop in Late Renal Allograft Dysfunction** July 15, 2004
- **Site-specific Approaches on the Prevention or Management of Pediatric Obesity** July 14-15, 2004

- **Preparing for a Career in Clinical Research in Kidney and Urologic Diseases**
  July 9-10, 2004
- **Modifiable Environmental and Behavioral Determinants of Overweight among Children and Adolescents**
  June 22-23, 2004
- **FDA/NIH Joint Symposium on Diabetes: Targeting Safe and Effective Prevention and Treatment**
  May 13-14, 2004
- **Lipids and the Pathophysiology of Obesity**
  May 10-11, 2004
- **Organ Innervation: Development, Disease, and Repair**
  April 15-16, 2004
- **Diabetes Mellitus Interagency Coordinating Committee (DMICC)**
  April 8, 2004
- **Immunobarriers for Pancreatic Islet Transplantation**
  March 29-30, 2004
- **Adipose Tissue Secretory Function and Its Role in Obesity-associated Co-morbidities**
  December 11-13, 2003
- **Urologic Complications in Diabetes**
  December 3-4, 2003
- **Phenotyping Obesity for Human Genetic Studies**
  October 28–30, 2003
- **Research Insights into Interstitial Cystitis: A Basic and Clinical Symposium**
  October 30–November 1, 2003
- **Epidemiology of Interstitial Cystitis Task Force**
  October 29, 2003
- **Diabetic Complications: Progress through Animal Models**
  October 20–21, 2003
- **NIDDK Network of Minority Research Investigators (NMRI) Workshop**
  May 1–2, 2003
- **Imaging the Pancreatic Beta Cell**
  April 21–22, 2003
- **NIDDK New Investigators Workshop**
  April 7–8, 2003
- **Metabolic Imprinting and the Long-term Complications of Diabetes Mellitus: Bench to Bedside and Back 20th Anniversary of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications Study (EDIC)**
  April 10–11, 2003
- **Workshop on Cardiovascular Disease in Chronic Kidney Disease: Options for Intervention**
  March 10–11, 2003
- **Renal Clinical Trials Network Consortium**
  February 4–5, 2003
- **Biology of the Aging Kidney Workshop**
  January 23–24, 2003
- **The Interaction of Physical Activity and Nutrition: Biological Remodeling and Plasticity**
  December 8–10, 2002
- **Diabetes Prevention in American Indian Communities: Turning Hope Into Reality**
  December 10–13, 2002
- **NIDDK Joint New Investigators and Network of Minority Research Investigators Workshop**
  November 7–8, 2002
- **Hepatitis C and Renal Disease**
  October 21–22, 2002

Health Disparities among Special Populations of Women

Research Efforts to Reduce Health Disparities in NIDDK Diseases

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high priority research areas for the NIDDK. These include type 2 diabetes, obesity, nutrition-related disorders, hepatitis C, gallbladder disease, *H. pylori* infection, sickle cell disease, kidney diseases, and metabolic, gastrointestinal, hepatic, and renal complications from infection with HIV. Moreover, some of these diseases affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination (OMHRC) oversees institute efforts to address these disparities. The OMHRC has recently updated the NIDDK Strategic Plan on Minority Health Disparities to highlight efforts under way; the plan is available at *http://www.niddk.nih.gov/federal/planning/mstrathealthplan.htm*. One of these efforts meant to strengthen research in this area is a recently launched initiative encouraging health disparity research in diseases within its purview to reduce the human and economic costs resulting from inequities in health care and health outcomes.

Information and Education Efforts to Reduce Health Disparities

Several new or enhanced NIDDK-supported informational activities also address minority health disparities:

- **Diabetes**
  In 2004 the National Diabetes Education Program (NDEP) launched the first national multicultural type 2 diabetes prevention campaign, with tailored materials and messages for high-risk audiences. Campaign materials include motivational tip sheets, as well as print and radio public-service ads. For African Americans, the NDEP's campaign, More Than 50 Ways To Prevent Diabetes, uses humor to encourage healthy lifestyle changes. For a Hispanic audience, the NDEP launched the campaign, Prevengamos la Diabetes Tipo 2: Paso a Paso (Let's Prevent Type 2 Diabetes: Step by Step). Campaign materials include a music CD, performed by Hispanic recording artists, to promote physical activity. For American Indians and Alaska Natives, the NDEP launched the public awareness campaign, We Have the Power To Prevent Diabetes. The campaign uses testimonials from American Indians and Alaska Natives who have made lifestyle changes to prevent diabetes. For Asian Americans and Pacific Islanders, the NDEP's campaign, Two Reasons I Find Time To Prevent Diabetes . . . My Future and Theirs, uses an intergenerational appeal to encourage people to make healthy lifestyle changes. The NDEP also is reaching out to older adults with the campaign, Its Not Too Late To Prevent Diabetes. Take Your First Step Today. To help promote the campaign, NDEP has assembled a team of people from across the country working to prevent diabetes in their own lives and in their communities. Further information can be found at *http://ndep.nih.gov/campaigns/SmallSteps/SmallSteps_index.htm*. The NDEP is jointly sponsored by the NIDDK and the Centers for Disease Control and Prevention, and works in partnership with public and private groups on efforts to improve the treatment and outcomes for people with diabetes, to promote early diagnosis and, ultimately, to prevent the onset of diabetes.

- **Obesity**
  It is estimated that over 77 percent of adult African American women are overweight or obese, using the body mass index (BMI) measurement—placing them at risk for many serious health complications. The Weight-control Information Network (WIN) program, Sisters Together: Move More, Eat Better, is a national initiative that encourages African American women to maintain a healthy weight by becoming more physically active and eating more healthful foods. Among its publications are: *Celebrate the Beauty of Youth!*, which was published this past year, *Fit and Fabulous as You Mature*, *Energize Yourself and Your Family*, and *Walking . . . A Step in the Right Direction*. WIN is conducting an outreach effort to contact historically Black colleges and universities and various community venues to promote the availability of *Sisters Together* brochures.

- **Kidney Disease**
  Racial and ethnic minorities suffer a far greater incidence and prevalence of irreversible kidney failure than Caucasians. Rates of end-stage renal disease (ESRD) are disproportionately greater in African Americans, American Indians and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans. Diabetic kidney disease is the most common cause of ESRD in all of the racial/ethnic minority groups in the United States, except for African Americans in whom high blood pressure-induced kidney damage is also a major cause. The NIDDK has launched a new information campaign, the National Kidney Disease Education Program (NKDEP). Currently, the NKDEP is targeting primary care providers and people at high risk for kidney disease—particularly African Americans with diabetes, high blood pressure, or a family history of kidney failure. In June 2004, the NKDEP nationally launched the campaign, You Have the Power to Prevent Kidney Disease, which emphasizes three key messages: 1) early detection is important; 2) effective treatment can prevent or slow kidney damage; and 3) left undiagnosed and untreated, kidney disease can lead to kidney failure. The message focuses on identifying risk factors for kidney disease, screening those at risk, and providing appropriate treatment for those who are diagnosed with kidney disease. The program plans to broaden its target audiences to include other at-risk audiences as the program expands. The ultimate goal of this educational campaign is to reduce complications and death due to kidney disease and kidney failure among all Americans.

National Institute of Environmental Health Sciences

Environmental agents likely play a role in a number of important female-predominant diseases. These include breast cancer, osteoporosis, ovarian dysfunction (e.g., premature menopause, polycystic ovarian syndrome, and ovarian cancer), uterine fibroids, and autoimmune diseases. The National Institute of Environmental Health Sciences' (NIEHS) approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds (both natural and synthetic) in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to determine the importance of the timing of exposure on disease risk. As results of these studies become available, women can better determine how to alter lifestyle factors leading to these diseases and environmental health regulators can better define standards that protect women from environmental triggers of these diseases.

Prevention and intervention efforts are major focuses of NIEHS activities. These efforts include hazard identification and characterization, both through traditional animal testing and epidemiologic studies and through incorporation of mechanistic considerations to arrive at new insights into the molecular basis of toxic effects. Although many people think of environmental exposures in terms of synthetic chemicals, the NIEHS also investigates natural compounds and the importance of diet and supplements in protecting health.

Identifying important triggers of disease is complicated by the fact that environmental exposures do not act in isolation. Underlying genetic susceptibilities, as well as the stage of life at which exposures occur, can have a profound effect on final disease risk. The NIEHS continues to investigate genetic susceptibilities to environmental disease risk and is spearheading the Environmental Genome Project that will help identify the important genetic variants of environmental response genes for both women and men. The importance of early exposures in later disease risk continues to be investigated both through individual laboratory studies and through the use of larger, life-time cohorts.

Working Groups Focused on Women's Health

The NIEHS' Laboratory of Women's Health focused on important diseases in women, such as breast cancer, ovarian cancer, uterine leiomyoma, ovarian dysfunction, and

pregnancy and parturition dysfunctions. The laboratory studied how these diseases develop and occur over the life span of a woman and how environmental toxins and stresses cause these diseases. The ultimate goal is to reduce the burden of environmentally related diseases. The laboratory initiated a clinical study, the Uterine Leiomyoma Longitudinal Intervention Study, designed to define the growth dynamics of uterine leiomyomas through time and to develop markers for growing and/or clinically relevant leiomyomas which will be important in future studies of the etiology, therapy, and prevention of these tumors. The Laboratory of Women's Health also worked to develop genetically defined animal models that provide links between molecular medicine, human epidemiology, and experimental studies. These models provide opportunities to identify key genes and signaling mechanisms of the reproductive systems that interact with the environment over time at different stages of life. The overall goal is to integrate genetics, endocrinology, immunology, pathology, epidemiology, and clinical research to study diseases in women in order to discover new ways to prevent environmentally related diseases.

Accomplishments

Breast Cancer

Regular Aspirin Use May Decrease Breast Cancer Risk

Aspirin has been used as a non-prescriptive pain reliever for over 100 years with current use equaling over 80 million tablets consumed in the United States every day. Not until the 1970s was the mechanism of action discovered. Aspirin was found to inhibit the production of proinflammatory prostaglandins. In the past two decades, regular aspirin use has been shown to be protective for heart disease, stroke, and colorectal cancer. Research during this period has also suggested that inhibition of prostaglandin synthesis may prevent cancer. Cyclooxygenase (COX) is involved in the synthesis of prostaglandins. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are known to block the active site of COX and, therefore, inhibit prostaglandin production. The final reaction in the synthesis of estrogen is dependent upon a cytochrome P450 enzyme that is stimulated by prostaglandin E2. Therefore, inhibition of prostaglandin production will also decrease the production of estrogen. Given the importance of estrogen in the development of breast cancer, these investigators undertook an epidemiologic study to determine whether regular NSAID use protected against breast cancer. Regular aspirin use was associated with a reduction in breast cancer risk in patients with hormone-responsive tumors. The results were stronger for women who took seven or more aspirin tablets per week. The results of Ibuprofen use were generally weaker. There was no reduction in risk among women who took acetaminophen, which does not inhibit prostaglandin synthesis. This study adds to the growing body of data that supports the regular use of aspirin as an effective chemopreventive agent for hormone-responsive breast cancer tumors. This effect most likely occurs through the inhibition of prostaglandin and subsequent inhibition of estrogen biosynthesis. The reduced risk must be confirmed by other researchers before clinicians can make definite recommendations to women at risk for breast cancer, but this and other studies do provide evidence of a protective effect.

Tamoxifen and Estrogen Induce Chromosome Breaks in DNA Repair-deficient Cells

Tamoxifen is widely used as an antiestrogen therapy for breast cancer patients and as a chemopreventive agent for healthy women at high risk for breast cancer. Highlighting the complexity of its actions, tamoxifen use has been associated with increased incidence of endometrial cancer in humans and has been shown to cause liver cancer in laboratory animals. It has been characterized as a human carcinogen by the International Agency for Research on Cancer. The estrogen derivative, 17 β-estradiol (E2) also possesses carcinogenic activity. Research has suggested that tamoxifen and E2 may be carcinogenic through tumor initiation or promotion. Both agents bind to the estrogen receptor which regulates specific genes. Tamoxifen and 4-hydroxyestradiol, a metabolite of E2, readily form DNA adducts. However, the contribution of these adducts to the carcinogenic potential

of both agents remains unclear. Using a cell culture system deficient in DNA repair pathways, the NIEHS-supported team explored the molecular mechanism of tamoxifen-induced mutagenesis. The cells were found to be hypersensitive to tamoxifen exhibiting an increase in chromosomal breaks and were also sensitive to 4-hydroxyestradiol. The researchers determined that the major deficient DNA repair mechanism responsible for these effects was a process known as translesion DNA synthesis. These results, combined with previous results from this laboratory, indicate that this cell system is a reliable model for analysis of the genotoxicity of estrogen- or tamoxifen-related products. Furthermore, the model might prove useful for characterization of the potential mutagenic activities of other agents that induce DNA replication damage and blocks. The researchers conclude that a "better understanding of tamoxifen-dependent mutagenesis may contribute to development of new drugs for the treatment or prevention of breast cancer with higher therapeutic efficacy and reduced genotoxicity."

Cell-specific Responses to Chemotherapy Agents in Breast Cancer

Microarray gene expression profiling has recently been used to identify specific subtypes of breast cancer tumors that originate in different cell types and show differences in patient outcome. Breast tumors respond variably to chemotherapeutic agents, such as doxorubicin and 5-fluorouracil, and the responses are variable between patients as well. This team of NIEHS-supported scientists performed a series of microarray experiments to gain insight into the differing responses of different types of tumors to chemotherapeutic agents. Four different breast cancer cell line cultures from two different cell types (basal and luminal epithelial cells) were treated with doxorubicin and 5-florouracil. Changes in gene expression were determined using microarray analyses. The overarching response in each of the cell lines was a general stress response, but distinct expression patterns were observed. Luminal cell lines tended to repress cell cycle-regulated genes and other genes involved in cellular proliferation. On the other hand, basal cell lines repressed genes involved in differentiation. The *in vitro* responses were then compared to expression responses in actual breast tumors sampled before and after treatment with the two drugs. The *in vivo* data matched well with the *in vitro* data with the cell-type-specific responses being very similar. The similarity between the *in vivo* and *in vitro* response has implications for understanding the biological responses to the chemotherapeutic agents. These results may also help to identify new agents for treatment of breast cancer. In addition, the specific mechanisms of action of doxorubicin and 5-flurouracil may be evident in a subset of genes. Subsequent analyses will attempt to identify these specific genes.

Estrogen Regulation of Antioxidant Response Element-dependent Gene Expression

Exposure to chemicals that cause oxidative stress can greatly affect the development of many diseases, including cancer. The metabolism of many chemicals has proven to be effective in modulating the degree of oxidative damage. The metabolism of many chemicals involves two distinct types of enzymes known as phase I and phase II. Phase I enzymes, members of the cytochrome P450 superfamily, metabolically oxidize many chemicals thereby forming intermediates. Phase II detoxification enzymes, such as glutathione-s-transferases and quinone reductase, which are responsible for metabolizing the products of phase I metabolic reactions, degrade these reactive intermediates by conjugation or reduction reactions, thereby protecting cells from oxidative DNA damage. Understanding how estrogens regulate phase II detoxification enzymes is important in explaining how estrogen exposure increases the risk of developing certain cancers like breast cancer. Phase II enzyme expression is regulated by a DNA sequence known as the antioxidant response element. These researchers sought to determine whether 17β-estradiol could regulate the antioxidant response element-dependent gene expression. Results indicate that estradiol did repress glutathione gene expression. Additionally, glutathione and quinone reductase activities were significantly lowered in a dose-dependent manner after estradiol exposure in the uteri of mice. These experiments conclude that 17β-estradiol and other estrogens downregulate phase II enzyme activities. This repression may increase cellular oxidative DNA damage that ultimately can

result in the formation of cancer in estrogen-responsive tissues like the breast and female reproductive organs.

Residential Magnetic Field Exposure and Breast Cancer Risk

Experimental and epidemiologic evidence suggests that residential exposure to power-frequency magnetic fields can increase breast cancer risk. This association was investigated in a breast cancer study in African American, Latina, and Caucasian women in Los Angeles County, California. Exposure was assessed using wiring configuration coding (an indirect measure of magnetic field exposure) and by direct measurement of magnetic fields. Researchers found no indication that breast cancer risk was increased by higher exposure to magnetic fields, as assessed either by direct measurements or indirectly via wiring configuration coding. We also found no evidence of an association of either broadband or harmonic magnetic fields and breast cancer. The results of this study indicate that residential magnetic field exposures commonly experienced by U.S. women do not influence the risk of breast cancer.

Intervention to Delay/Prevent Breast Cancer

Animal models are useful for understanding the biology of breast cancer and for evaluation of prevention strategies and therapeutic approaches. Phytoestrogens, such as isoflavonoids and lignans, have been postulated as breast cancer protective constituents in soy and whole-grain cereals. Researchers investigated the ability of isoflavones (IFs) and flaxseed to modulate spontaneous mammary tumor development in female heterozygous Tg.NK (MMTV/c-neu) mice. Two different exposure protocols were applied, either from 4 weeks of age onward (postweaning) or during gestation and lactation (perinatal). In the postweaning exposure study, mice were fed IFs or flaxseed in a high-fat diet. In addition, flaxseed in a low-fat diet was tested. Postweaning exposure to IFs and flaxseed tended to accelerate the onset of mammary adenocarcinoma development, although tumor burden at necropsy was not changed significantly. Perinatal IF exposure resulted in enhanced mammary gland differentiation, but palpable mammary tumor onset was not affected. However, tumor burden at necropsy in the perinatal exposure study was significantly increased in the medium- and high-IF dose groups. Comparison of both exposure scenarios revealed a strongly accelerated onset of tumor growth after perinatal high-fat diet exposure compared with the low-fat diet. This study shows that breast cancer-modulating effects of phytoestrogens are dependent both on the background diet and on the timing of exposure in the life cycle.

The Sister Study: Environmental and Genetic Risk Factors for Breast Cancer

The NIEHS Sister Study will prospectively examine environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. Such sisters have twice the risk of developing breast cancer as other women. The frequency of any relevant genes and shared risk factors will also be higher, enhancing the statistical power of the study to detect risks. Sisters are expected to be highly motivated and response rates and compliance over time are expected to be high. Thus, studying sisters will enhance our ability to understand the interplay of genes and environment in breast cancer risk and to identify potentially preventable risk factors. The prospective design will allow us assess exposures before the onset of disease, thus avoiding biases common to retrospective studies and aiding in causal interpretation. The study will create a framework from which to test new hypotheses as they emerge. Recruitment strategies will maximize inclusion of minorities and high-risk women. Blood, urine, and environmental samples are collected and banked for future use in nested studies of women who develop breast cancer (or other diseases). The cohort will be followed prospectively for 10 or more years. Medical history and vital status will be updated annually and changes in exposures will be assessed at 2-year intervals. Medical records and tumor tissue (if feasible) will be retrieved for those who develop cancer. Medical records will also be sought to facilitate the study of other diseases of importance to women. Analyses will assess the independent and combined effects of environmental exposures and genetic polymorphisms that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential

risk factors (e.g., smoking, occupational exposures, alcohol, diet, obesity) and include measurement of phthalates, phytoestrogens, and metals in blood and urine, insulin, growth factors, vitamins and nutrients, and genes. The cohort will also be used to study risk for other diseases (e.g., heart disease, osteoporosis, other hormonal cancers, autoimmune diseases), as well as explore genetic and environmental effects on prognosis. A pilot phase began August 2003 involving women from four metropolitan areas of the United States selected for their geographic and ethnic diversity in order to assess a range of recruitment strategies and plan for a larger-scale national effort. Enrollment later expanded to include those four states and, in August 2004, four additional state were added. National recruitment began on October 18, 2004.

Identifying Environmental Triggers of Breast Cancer—The Agricultural Health Study

The Agricultural Health Study is a collaboration between the NIEHS, the National Cancer Institute (NCI), and the U.S. Environmental Protection Agency (EPA). This study explores potential causes of cancer and other diseases among farmers and their families and among commercial pesticide applicators. The Agricultural Health Study is a prospective study of 55,000 licensed pesticide applicators and nearly 35,000 spouses of farmer applicators. Originally developed by the NCI to examine cancer risks, the scope of the project was expanded with funds from the NIEHS to include a multitude of other health endpoints, including those with particular relevance to women. The benefits of this study extend beyond farmers because the exposures under study (e.g., pesticides, solvents, nitrates, metals, mycotoxins, silica) are not limited to farmers, but are common to rural communities and other settings. Enrollment of the cohort has been completed, with more than 80 percent of eligible applicators in Iowa and North Carolina completing a questionnaire about their exposures and health status. Cohort members are now completing 5-year follow-up interviews; cancer incidence and mortality are being evaluated using cancer registries and vital records. The NIEHS has identified possible links between farm exposures and some neurological health endpoints. A NIEHS-supported researcher was studying the herbicide, paraquat, which acts adversely on the dopamine system. When paraquat and the fungicide, maneb, were jointly administered to mice, the combined exposure decreased motor activity, increased dopamine turnover, and reduced other measures of dopamine effect at levels far greater than when the same chemicals were administered individually. The fact that combined exposures, such as would be found in realworld applications, can potentiate the adverse effects on the dopamine system raises important possibilities for multiple environmental risk factors being associated with Parkinson's disease development. This work is complemented by another group of federally supported researchers. They found that the organic pesticide, rotenone, produced symptoms of Parkinson's disease in laboratory animals. Women's health endpoints being examined by the NIEHS include premature ovarian failure, uterine fibroids, endometriosis, systemic lupus erythematosus, and menstrual function. Other disease risks being studied are thyroid disease, diabetes, childhood growth and development, asthma and altered lung function, immunologic response, degenerative eye diseases, and neurodegenerative and neurobehavioral effects. A nested study of farming-related and other risk factors for Parkinson's disease is being developed in collaboration with researchers from the Parkinson's Disease Institute. Additionally, the NIEHS is investigating other ways of enhancing this study such as: 1) collecting blood and urine from the entire cohort to allow exposure assessment in future studies, 2) analyzing well water samples for nitrates, and 3) monitoring exposure to pesticides and other agents in specific subsets of the cohort.

Ovarian Cancer

Ovarian cancer is the most fatal of the gynecological cancers, with 28,000 new cases reported yearly in the United States.

Ovarian Cancer Risk and Use of Phenolphthalein-containing Laxatives

Experimental studies in rodents demonstrated the carcinogenic potential of phenolphthalein, the active ingredient in some laxatives, administered at doses similar to the dose that could be used by humans. Ovarian cancer was one

of the cancers observed in these studies. We examined the association between epithelial ovarian cancer and use of phenolphthalein-containing laxatives in a population-based, case-control study. Compared to women who never used a laxative, past or present use of a phenolphthalein-containing laxative was not associated with an increased risk of invasive ovarian cancer or of borderline ovarian cancer. Total days used, mean number of pills per day, and cumulative dose were also unrelated to risk. This study provides some assurance that phenolphthalein-containing laxatives do not increase the risk of ovarian cancer in humans. These findings are of particular importance to those countries in which phenolphthalein is still used in over-the-counter medications.

Cyclooxygenase-1 and -2 in Normal and Malignant Human Ovarian Epithelium

Cyclooxygenase-1 and -2 (COX-1 and COX-2) play important roles in normal physiology and are often dysregulated in neoplastic tissues. The present study determines whether COX-1 and COX-2 are expressed in ovarian cancers and whether the pattern of expression of these enzymes reveals clues to their roles in this cancer. COX-1 protein was present in 95/137 (69.3 percent) of the total cancers studied, with 55/83 (66.3 percent) of the primary cancers and 40/54 (74.1 percent) of the metastatic cancers positive for protein. COX-2 was present in 97/137 (70.8 percent) of all cancers studied, with 53/83 (63.9 percent) of the primary cancers and 44/54 (81.5 percent) of the metastatic cancers positive for protein. Notably, the quickscores for COX-2-positive staining were significantly higher in metastatic cancers. Moreover, COX-2 immunostaining was frequently found at the advancing margin of tumor invasion or in new metastatic loci. COX-1 protein expression was observed in the ovarian surface epithelial cells, especially that of the inclusion cysts. COX-1 was also detected by western blot in seven of nine ovarian cancer cell lines. However, no COX-2 was detected in either normal epithelium or cancer cell lines. COX-1 and COX-2 were expressed in every type of ovarian epithelial cancer, suggesting that each may contribute to the cancer development or progression.

Frequency of Intercourse Around Ovulation: Evidence for Biological Influences

Intercourse in mammals is often coordinated with ovulation, for example through fluctuations in libido or by the acceleration of ovulation with intercourse. Such coordination has not been established in humans. We explored this possibility by examining patterns of sexual intercourse in relation to ovulation. The frequency of intercourse rose during the follicular phase, peaking at ovulation, and declining abruptly thereafter. The 6 consecutive days with most frequent intercourse corresponded with the 6 fertile days of the menstrual cycle. Intercourse was 24 percent more frequent during the 6 fertile days than during the remaining non-bleeding days. There apparently are biological factors that promote intercourse during a woman's 6 fertile days.

Menstrual Patterns, Menopause, and Women's Health

Ovarian function (encompassing the cyclical production of estrogen and progesterone during the reproductive years and the timing of ovarian failure or menopause) plays an important role in women's health. Menstrual cycle patterns may reflect hormonal status, and specific menstrual characteristics, such as cycle length or variability, may directly or indirectly affect the risk of developing hormonally mediated diseases, such as osteoporosis. Menopause represents a normal aspect of aging, but it also influences risk for a wide variety of diseases. Studies have reported increased mortality risk with early natural menopause, and age at menopause has been proposed to be a marker of aging and health. The causes and consequences of early menopause is another important focus of this project. Potential endocrine-disrupting chemicals are particularly relevant to the mission of the NIEHS, and this project incorporates the study of such exposures. The specific studies that have been completed or are currently underway within this project include: 1) Menstrual Cycle Patterns in Relation to Risk of Chronic Diseases—analyses using prospectively collected menstrual cycle data from over 800 women followed from their 20s through menopause. The specific health

conditions examined in relation to menstrual cycle patterns include heart disease, diabetes, perimenopausal fracture risk, and total mortality. 2) Menopausal Status and the Menopausal Transition—analyses using national population-based studies (the National Health and Nutrition Examination Survey III and the National Health Information Survey), including methodologic research comparing different analytic methods for assessing associations with timing of menopause. 3) Pesticide Exposure, Menstrual Cycle Characteristics, and Timing of Menopause—analyses using the Collaborative Perinatal Project, the Agricultural Health Study, and a newly designed longitudinal study examining biological measures of DDE and PCB exposure in relation to timing of natural menopause This third set of studies was prompted by the recognition of the endocrine-disrupting and ovotoxic potential of specific pesticides, a topic of particular interest to the NIEHS. Despite the evidence from toxicology studies, there has been little effort on the part of epidemiologic studies to examine the ovarian-related effects of organochlorines and other environmental contaminants.

Endometrial Cancer

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the United States but remains the least studied of the major cancers affecting women. Unlike cancers of the breast and ovary, endometrial cancer is limited primarily to women over the age of 50, and well-established risk factors suggest probable etiologic factors, most relating to estrogen. Researchers at the NIEHS are using molecular genetic approaches to distinguish etiologic factors and animal models (including transgenic mice) to understand the role of physiologic and environmental factors in endometrial carcinogenesis. Endometrial cancer is being investigated in the Sister Study.

The Eleventh Report on Carcinogens

The Eleventh Report on Carcinogens, prepared by the National Toxicology Program at the NIEHS, lists steroidal estrogens as known human carcinogens for the first time. These are a group of related hormones that control sex and growth characteristics and are commonly used in estrogen replacement therapy to treat symptoms of menopause and in oral contraceptives. The report cites data from human epidemiology studies that show an association between estrogen replacement therapy and a consistent increase in the risk of endometrial cancer and a less consistent increase in the risk of breast cancer. As for the other common use for steroidal estrogens, the report says the evidence suggests estrogen-containing oral contraceptives may be associated with an increased risk of breast cancer but may protect against ovarian and endometrial cancers.

Genotoxicity of Estrogen- and Anti-estrogen-DNA Adducts

Tamoxifen, an antiestrogen used in the endocrine therapy and chemoprevention of breast cancer, induces liver cancer in rodents and is associated with endometrial cancer in women. Estrogens also are implicated in the etiology of endometrial and breast cancer. The carcinogenicity of these agents may be mediated through their genotoxic effects. The goals of this research are to establish a mechanism for the genotoxicities of tamoxifen and estrogen and to find a safer alternative to tamoxifen. Using site-specifically modified oligodeoxynucleotides, the mutagenic and repair potential of estrogen and antiestrogen DNA adducts in mammalian cells will be determined. The three-dimensional structure of tamoxifen and estrogen adducts in DNA duplex also will be established, permitting us to understand the process of mutagenic and repair events which occur at lesion sites. Such modified oligodeoxynucleotides also will be employed as standards in ultrasensitive 32P-postlabeling and HPLC/electrochemical detector analyses designed to quantify DNA adducts and oxidatively damaged lesions in the tissues of rodents and monkeys treated with these drugs. Taken together, this information can be used to predict genotoxicity. Translational studies have been designed to detect adducts in the endometrial DNA of patients undergoing treatment with tamoxifen or toremifene. These experiments will provide biomarkers for molecular epidemiological studies and explore the relationship between tamoxifen therapy and the development of endometrial cancer in women treated with this drug. This research should lead to a safer alternative for women undergoing breast cancer therapy and for chemoprevention.

Endometriosis

In Utero PCB Exposure and Endometriosis

Endometriosis is a relatively common disease (prevalence estimated at 5 to 10 percent) that can affect fertility, as well as other aspects of a woman's general health and well being. Animal and human data suggest that the critical exposure window for endocrine disruptors may be *in utero* because the developing fetus is extremely sensitive to endocrine hormones during reproductive development. A case-control study nested in the National Collaborative Perinatal Project (NCPP) cohort, will extend followup through the reproductive years of the daughters of the pregnant women recruited in the NCPP (1959 to 1966). During pregnancy, one or more blood samples were taken from the pregnant women and archived. The daughters will be traced and will complete a question on endometriosis and menstrual cycle characteristics. Cases are daughters with laparoscopy-confirmed endometriosis. Blood samples will be analyzed to reflect adult PCB levels that may confound the relationship between endometriosis and *in utero* PCB exposure, and will serve as a source of additional information on cumulative exposure.

Serum TCDD Levels and Endometriosis

Dioxin, a ubiquitous contaminant of industrial combustion processes including medical waste incineration, has been implicated in the etiology of endometriosis in animals. A population-based historical cohort study was conducted 20 years after the 1976 factory explosion in Seveso, Italy resulted in the highest known population exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The relation of serum TCDD levels to fertility (time to conception and clinical infertility); ovarian function (number of ovarian follicles, presence of functional ovarian cysts, serum hormone levels); uterine health (uterine volume, endometrial thickness, and the occurrence/number of fibroids); the occurrence of benign breast disease; and the initiation/duration of lactation in the Seveso cohort are being investigated. Pre- or post-menarche exposure to TCDD is also being evaluated.

Uterine Fibroids

Uterine fibroids are benign (noncancerous) tumors that are present in the muscular wall of the uterus in up to 70 percent of all women. They are the leading cause for hysterectomy in the United States. Even though they are benign, fibroids sometimes cause reproductive problems, such as heavy bleeding, pelvic pressure, severe cramping, pain, infertility, and miscarriage. Little information is available about why fibroids develop or why they grow. Some evidence suggests that it may be related to a genetic problem. It is also possible that fibroids may grow in response to environmental factors, such as diet, smoking, exercise, or exposure to certain chemicals.

NIEHS Uterine Fibroid Study

Despite the morbidity and high medical costs associated with fibroids, there has been little epidemiologic study of this condition. Indications are that African American women are at higher risk, but because this supposition is based on hysterectomy statistics, it is not known if this is a true difference or is due to differences in diagnosis and treatment. The NIEHS Uterine Fibroid Study, a cross-sectional epidemiological study of uterine leiomyomas in women ages 35 to 49, randomly selected from membership in a prepaid health plan in Washington, DC, was initiated to better define the cause of this health disparity. The prevalence of ultrasound-detected fibroids was surprisingly high, especially in the African American participants: 72 percent for African American and 50 percent for Caucasian women. Health disparity issues for uterine fibroids are reflected in the high prevalence statistics and in the fact that African American women have larger and more numerous tumors. African American women are also more likely to have surgical interventions, such as myomectomy and hysterectomy, compared to Caucasian or Hispanic women.

Uterine Fibroid Growth Study

The Fibroid Growth Study is designed to investigate why some fibroids grow to become health problems while others do not. Funding is provided jointly by the NIEHS and the National Center for Research on Minority Health and Health Disparities (NCMHD).

Scientific direction and oversight are provided by the NIEHS. The University of North Carolina Hospitals, the General Clinical Research Center, and the Integrated Laboratory Systems, Inc. are collaborators in this research. The study has four specific aims. First, fibroid growth will be evaluated over time by magnetic resonance imaging (MRI). Second, the relationship between fibroid growth and symptoms or outcomes (i.e., surgery/no surgery) will be determined. Third, identify markers that may be related to growth. Lastly, examine the hormone and lifestyle factors that may be related to fibroid growth. It is hoped that the findings from this study will help develop strategies to prevent fibroids in women at high risk for problems and develop new therapies that reduce the need for radical surgical procedures like hysterectomy.

Environmental Estrogens and Fibroids—*In Vitro* Human and Mouse Comparison

The NIEHS Comparative Pathobiology Group has focused its research on defining the pathogenesis/carcinogenesis of disorders affecting the reproductive tract of humans and rodents, and assessing the role of environmental and endogenous factors in the induction of these disorders. Data show that transforming growth factor alpha (TGF-α) is expressed exclusively in malignant uterine smooth muscle cell tumors (leiomyosarcomas) of mice. However, in benign uterine smooth muscle cell tumors (leiomyomas) of mice and women this growth factor is not present. In mice, a positive correlation between TGF-α staining and immunoexpression of epidermal growth factor receptors and increased cell proliferation as measured by the expression of proliferating cell nuclear antigen (PCNA) in the malignant uterine leiomyosarcomas was observed. In women, we have found that IGF-I is overexpressed in unterine leiomyomas compared to normal myometrium during the proliferative phase of the menstrual cycle, and it appears that the IGF-I receptor signaling pathway is important in uterine leiomyoma growth. Studies to assess the role of Bcl-2 and Bax in modulating cell survival and death in human uterine leiomyomas have been conducted. The results show that both positive and negative regulatory proteins of programmed cell death (apoptosis) are present in human uterine leiomyomas, and that altered apoptosis does not appear to play a significant role in the development of these tumors through prolonged cell survival. Human uterine leiomyoma and normal smooth muscle cell lines have been successfully immortalized by the insertion of the human telomerase gene. *In vitro* model systems for studying uterine leiomyomas are limited in that human-derived leiomyoma cells grow poorly in culture and begin to senesce early. This obstacle has been overcome with the creation of an hTERT uterine leiomyoma cell line. Uterine leiomyoma tumorigenesis can be studied in a prospective manner using these immortalized cell lines.

Uterine Smooth Muscle Tumors in Pot-bellied Pigs Resemble Human Fibroids: A Potential Animal Model

Uterine leiomyomas (fibroids) clinically affect approximately 25 percent of women of reproductive age in the United States, with a subclinical incidence as high as 77 percent. The pathogenesis of fibroid formation remains poorly understood, due in large part to the lack of a suitable animal model. This retrospective study characterizes the clinical, gross, and histopathologic features of similar, spontaneously occurring uterine tumors in pot-bellied pigs. Pigs presented with clinical signs including abdominal distension or vaginal bleeding or were subclinical and identified during ovariohysterectomy. Tumors ranged from microscopic to 45 kg, were often multiple, and primarily involved the uterine horns. The cellular pattern/morphology and variable degree of fibroplasia of the fibroids were similar to that reported for human fibroids. These results support further investigation of fibroids in pot-bellied pigs as a potentially valuable animal model for studying human fibroids. Development of an animal model will be a very useful tool in investigating the causes of fibroids, fibroid pathogenesis, developing new treatment strategies, development and testing of new therapies, and development of preventive strategies.

Menopause

Genetic Differences and Effects on Exercise-induced Fat Loss in Postmenopausal Women

Many research studies have shown that postmenopausal women with high body fat content and high body mass index (BMI) are at increased risk of developing chronic diseases such as coronary heart disease, stroke, type 2 diabetes, colorectal cancer, and breast cancer. Strategies to reduce body fat content and obstacles to weight reduction are important factors to identify to aid in preventing these serious illnesses. These authors have previously shown that women who participated in a year-long, moderate-intensity exercise intervention reduced their BMIs and lost body fat compared to women who maintained a sedentary lifestyle. There were differences in the amount of body fat and weight reduction that might be explained by variability in genes involved in estrogen and androgen production. To test this new hypothesis, researchers enrolled 50- to 75-year-old postmenopausal women in a 225 minutes/week moderate exercise program for 1 year. Genetic polymorphisms for two genes, CYP19 and COMT, involved in the conversion of estradiol into testosterone or less active metabolites were examined. Exercisers with the CYP19 polymorphism had a larger decrease in total fat (7 pounds lost vs.1 pound) and percentage body fat (2.4 percent for 0.6 percent). Those women with the COMT polymorphism had a smaller decrease in percentage body fat. These results suggest that genetic polymorphisms in at least two genes, CYP19 and COMT, may be important for body fat regulation. Specifically, these gene forms may influence the effect of exercise on fat loss in postmenopausal women. This finding is significant because fat loss is important for lowering the risk of several chronic diseases.Knowing a person's polymorphic status for these two genes could explain why some women lose more weight than others in response to exercise and could alter the weight loss approach or warrant other interventions.

Osteoporosis

Osteoporosis is a debilitating condition characterized by fragility of the bone. It sometimes occurs in men, but is generally found in postmenopausal women. NIEHS-supported studies are investigating the effects of environmental lead exposures and allelic variants of the vitamin D receptor (VDR) gene on the development of osteoporosis in middle-aged women, and the health consequences of lead released into the blood stream and soft tissue due to osteoporosis. One health effect that has been identified is an increased risk for hypertension. Some of these studies are using lead as a marker to develop hormonal therapies to prevent bone reabsorption.

Lead Toxicity in the Skeleton and Its Role in Osteoporosis

This program project grant application seeks to define the mechanisms of lead (Pb) toxicity in the skeleton. The investigators have evidence that the adverse effects of this heavy metal on bone and cartilage function contribute to diseases, such as osteoporosis, and hinder osteoporotic fracture healing. The program project is made up of four projects, two of which are cellular and molecular in nature, one is animal-based, and one is clinical. Two cores are also proposed, an Administrative Core and a Histopathology Core.

- **Project 1: Molecular mechanism of lead's effect on osteoclasts and osteoblasts**
  This project will examine how Pb influences the key regulatory genes controlling bone resorption and bone formation. Preliminary data have implicated osteoprotegrin (OPG), RANK ligand, and TRIP as the genes responsible. The project will have both *in vitro* and *in vivo* components.

- **Project 2: Cellular and molecular effects of lead on chondrogenesis and cartilage differentiation**
  This research seeks to demonstrate that primordial regulators of chondrogenesis and cartilage differentiation (i.e., the BMP's Indian hedgehog, PTHrP, etc.) are influenced in a complex way by Pb. Lead exposure leads to inappropriate skeletal development and predisposes affected individuals to osteoporosis.

- **Project 3: Lead effects on skeletal stem cells and fracture healing**
  Project 3 will use an animal model to document that the findings in Project 1 and 2 are manifested *in vivo*. Additionally, this work will characterize the mechanism of the effect of Pb on hindering normal fracture healing.

- **Project 4: Clinical diagnostic and therapeutic approaches to skeletal lead toxicity**
  This project extends the basic science investigations into a clinical trial. It seeks to determine if therapeutic approaches for osteoporosis are effective in Pb-containing skeletons and in controlling blood Pb levels. This program project will define novel molecular pathways to explain the adverse effects of Pb on bone and cartilage. The pathways will be examined and validated in animals, and ultimately the findings will be translated into clinical trials. This program project provides the opportunity to investigate the skeletal effects of Pb from "the bench" to the "bedside." It is unique in this regard.

The Osteotoxicology Research Core: A New Addition to the University of Rochester Environmental Health Sciences Center

The goal of this core is to generate basic information on how environmental, occupational, and foreign agents adversely affect skeletal tissues, and how these effects impact quality of life. The five major projects within the core surround the themes of: 1) toxicology of the adult skeleton, 2) toxicology of the developing skeleton, and 3) toxicological effects of metals in oral biology. Specifically, these projects include the following: 1) the effects of lead on bone remodeling *in vitro*, 2) animal models of lead-induced osteoporosis, 3) the effect of foreign wear debris in osteolysis around implants, 4) effect of lead on growth plate chondrocytes, and 5) environmental influences of dental caries.

Hormonally Active Agents

The NIEHS is supporting a number of studies investigating the potential health effects of hormonally active agents (HAAs) in the environment. HAAs are a diverse group of compounds that include plasticizers, polycholorinated biphenyls, many pesticides, and dioxins. These compounds are so pervasive that studies have shown them to appear in tissues in 95 percent of the U.S. population. The concern is that, when exposure occurs very early in life, these compounds have the potential to disrupt critical endocrine pathways with potential future effects on reproductive, neurological, and immunological systems. This possibility has been verified in the NIEHS rodent studies showing that early exposure to some pesticides resulted in reproductive, neurological, and immunological deficits later in life. These and other studies on the effects of early exposure to HAAs continue. Additionally, the NIEHS is collaborating with the Centers for Disease Control and Prevention (CDC) to assess what the actual, real-world exposures to HAAs are in a representative U.S. population. In a preliminary report, the distribution of a particular class of HAAs, the phthalate plasticizers, was assessed. It was found that although most scientific and regulatory attention has focused on two phthalates—di(2-ethylhexyl) phthalate and di-isononyl phthalate—actual human exposures indicate that three other, less common, phthalates (diethyl phthalate, dibutyl phthalate, and benzyl butyl phthalate) account for the greater exposures in the United States. Additionally, women of reproductive age (20 to 40 years) were found to have significantly higher levels of monobutyl phthalate, a reproductive and developmental toxicant in rodents, than other age and gender groups. Results of this exposure assessment study will help guide us in selecting compounds for future study.

Dietary Soy and Cancer

It is well known that mice genetically engineered to develop breast cancer will develop tumors earlier and in larger numbers when fed soy-based diets. This is a potential public health concern because soybeans are a major protein source in vegetarian diets, and many women consume soy products to reduce hot flashes and other symptoms of menopause. Increasingly, infants are also consuming large amounts of soy products in the form of soy-based infant formula and consumer products especially marketed to appeal to children.

Soy has a number of components that can either mimic or compete with the hormone, estrogen. Given the biological activity of plant estrogens (phytoestrogens), the potential exists for adverse, as well as beneficial, health effects. NIEHS-supported researchers have recently identified other areas of concern in consuming large amounts of soy. They discovered that phytoestrogens in the diet increased the incidence of vulvar carcinoma in mice. Mice were given one of three natural ingredient diets or two purified diets containing predetermined levels of the predominant phytoestrogens found in soy, daidzein, and genistein. The two purified diets had similar caloric values and differed only in their protein source—derived from either soy protein or milk protein (casein). At 3 months, mice on the soybean-supplemented diet had a significantly increased incidence of vulvar carcinomas compared to mice fed a milk-derived protein source. A similar correlation was found between tumor incidence and phytoestrogen levels in the three natural ingredient diets. In total, there was a significant correlation between the total daidzein and genistein levels in the five test diets and the incidence of vulvar carcinomas in mice.

Herbal Medicine

Botanical, or herbal, formulations continue to be a major focus of NIEHS interest in the dietary arena. Over one-third of the adults in the U.S. population use herbal medicines or products; the majority of the users are women. The herbal industry has grown substantially over the last 10 years, and it is now a multibillion dollar industry. Of the nearly 2,000 herbal products in use, only a few have been adequately tested for efficacy and toxicology. Since the FDA is not permitted, by law, to require pre-market testing by producers, herbal medicines are poorly standardized and consumers are not aware of potential adverse effects, particularly those effects that might arise following long-term use. Of particular concern are developmental and reproductive effects since herbal products are used frequently by women of childbearing age. Other concerns include immunological responses, cardiovascular diseases, cancer, and interactions among the many constituents of herbal medicines or with prescribed pharmaceuticals. The NIEHS and the Office of Dietary Supplements have funded the Center for Dietary Supplement Research to establish a broad base of scientific knowledge on botanicals and to scientifically determine their effectiveness, safety, and chemical properties.

Pregnancy

Birth Cohorts

Studies aimed at determining the adverse effects of low-dose exposures during fetal development are significantly complicated by the fact that many of these effects do not appear until much later in life. The best way to detect these prenatal effects in humans is through long-term epidemiologic studies that follow a child through the mother's pregnancy and into the later years of a child's life.

The Norwegian Mother and Child Study

The Norwegian Mother and Child Study is a cohort study of pregnant women and their children in Norway. The NIEHS is contributing to this effort by creating of a biological specimen repository to evaluate environmental exposures and health effects to pregnant women and their unborn children. As of August 31, 2004, 22,710 women had contributed biological samples (blood and urine) for the NIEHS portion of the study; 10,000 women were enrolled this fiscal year. These samples have been collected at 41 hospitals across Norway, including urban centers and the Arctic regions. The enrollment target is 50,000 women. At the current recruitment rate, we anticipate 30,000 women with blood and urine samples collected at 17-weeks gestation to evaluate for environmental exposures. During the past fiscal year, we resolved problems associated with sample shipment and handling. Working with the CDC, we identified the optimal means to prevent bacterial contamination of urine samples while still maintaining the analytes of future interest (phenols, phthalates, non-persistent pesticides, arsenic, mercury). These data will be of use to other investigators in large cohort studies and a manuscript is in preparation. In collaboration with Norwegian investigators, we are implementing a quality assurance experiment and protocol to assess storage conditions

for a variety of parameters. This will take 2 years to complete. Results of the initial quality assurance measures will be presented at a professional meeting in October 2004. We are currently designing a study to use the NIEHS samples and link to the questionnaire data from the mother and the Medical Birth Registry data to assess health.

Height and Risk of Severe Preeclampsia: A Study within the Danish National Birth Cohort

Preeclampsia shares a number of risk factors with cardiovascular disease (CVD). Women with recurrent preeclampsia or preeclampsia early in pregnancy reportedly have an increased long-term risk of CVD. Short stature is a risk factor for CVD, but has rarely been examined in relation to preeclampsia. We used data from 59,968 singleton live births in the Danish National Birth Cohort, born between 1998 and 2001, to assess risk of severe preeclampsia/eclampsia (296 cases) in relation to self-reported height. Short stature was associated with a higher risk of severe preeclampsia in multiparas participating in the Danish National Birth Cohort. Our study, if corroborated, adds a new piece to the puzzle of the aetiology of preeclampsia. An easily measured risk factor, such as height, may also be useful in identifying women at increased risk.

Lead in Breast Milk

Research has focused a great deal of attention on the risks for the developing fetus from circulating levels of lead in maternal blood, but much less attention has been given to the danger lead in breast milk may have on the cognitive development of young children. Although there are many well-recognized benefits of breast feeding for mothers and infants, there are no clear guidelines on breast feeding for women who have high circulating or bone levels of lead. Previous research has shown that maternal bone lead stores, from past environmental exposures, are mobilized during pregnancy and lactation as calcium stores are drawn upon. However, there is less information on the transfer of lead to breast milk. To investigate whether maternal stores of lead can be transferred to breast milk, this NIEHS-supported team performed an epidemiologic study with 310 lactating women in Mexico City, Mexico. Maternal blood, umbilical cord blood, and breast milk samples were analyzed for lead content. Maternal bone lead concentration was determined non-invasively. Levels of lead in breast milk ranged from 0.21 to 8.02 micrograms/liter with an average of 1.1 micrograms/liter. In comparison, maternal blood lead ranged from 18 to 300 micrograms/liter. A positive correlation existed between breast milk lead and blood lead level. The data show that for a rise of 50 micrograms of lead/liter of blood, the breast milk lead level rose 33 percent. Comparatively equal increases in bone lead content resulted in smaller increases in breast milk (14 and 5 percent for patellar lead and tibia lead, respectively). These results indicate that even among a population of women with relatively high lifetime exposure to lead, breast milk lead levels are low. These levels are influenced by both current exposures to lead, as well as the mobilization of lead from bone stores during pregnancy and lactation. There is no safe level of lead exposure; however, the authors conclude that despite the potential for lead exposure, breast milk is the most complete nutritional source for young infants.

Folic Acid Deficiency and Late Gestation Brain Development in Mice

Neural tube defects are known to be caused by folic acid deficient diets during the early stages of pregnancy. Women are routinely counseled to take folic acid supplements during the early weeks of their pregnancies. In previous work in laboratory animal studies, these researchers discovered the importance of maternal dietary choline intake late in pregnancy for proper development of the hippocampal region of the brain. Because choline and folate are metabolically interrelated, they speculated that folic acid may also be important at later stages. Pregnant mice were given either folate-supplemented, control, or folate-deficient diets from days 11 through 17 of their 21-day pregnancy. The folate-deficient diets decreased the number of neural progenitor cells undergoing cell division by up to 54 percent in three regions of the fetal brains. In addition the number of apoptotic cells in the fetal brains was two-times higher in

the fetal septum for the folate-deficient mouse pups. Pups from the folate-supplemented group did not differ from the control group. These results indicate that progenitor cells in fetal forebrains are sensitive to maternal dietary folate intake during late gestation. Applying these results to human pregnancy suggests that folate availability affects brain development long after neural tube closure, and indicates that it may be very important that women ingest adequate amounts of folic acid throughout pregnancy. This may be especially important in those women with genetic polymorphisms in genes of folate metabolism.

Drug Used to Arrest Preterm Labor Sensitizes the Brain to Neurotoxins

There is a growing body of evidence that suggests that exposure to environmental agents *in utero* or very early after birth can have life-long effects. This phenomenon is referred to as the fetal basis of adult disease. It is of growing concern to the NIEHS and environmental health scientists worldwide. Hypertension, diabetes, asthma, and cardiovascular diseases are but a few of the illnesses that have been suggested as possible effects from these early-life exposures. This investigator examined the combined exposures of terbutaline, a drug used to arrest preterm labor, and subsequent exposure to the organophosphate pesticide chlorpyrifos on several indices of brain cell growth and function. Young rats were given terbutaline on days 2 through 5 after birth, followed by chlorpyrifos on days 11 through 14. Neither treatment affected growth or viability of the young rats; however, both elicited alterations in brain cell differentiation and cholinergic innervation at day 15 persisting into adulthood (day 60). Biomarkers of brain cell number, cell size, and neuritic projections were affected by either agent alone; however, the combined exposure produced more severe effects. These findings suggest that terbutaline is a developmental neurotoxicant much like chloripyrifos. The authors conclude that the use of terbutaline to prevent preterm labor may be creating a subpopulation that is more sensitive to the adverse neural effects of organophosphate pesticides. Further studies are needed to repeat these findings, but if the results are confirmed, use of these compounds may need additional scrutiny.

Hormonal and Reproductive Risk Factors for Development of Systemic Lupus Erythematosus

Estrogen and prolactin may accelerate the progression of murine systemic lupus erythematosus (SLE). In humans, 85 percent of lupus patients are women, which also suggests the importance of hormonal factors in disease pathogenesis. The purpose of this study was to examine hormonal and reproductive risk factors for lupus among women participating in the Carolina Lupus Study. Breast feeding was associated with a decreased risk of developing lupus, with a statistically significant trend for number of babies breast fed and total weeks of breast feeding. There were no associations with number of pregnancies or live births. Natural menopause occurred earlier in women with subsequent development of lupus, compared with controls. There was little association between SLE and current use or duration of use of hormone replacement therapy or oral contraceptives, and no association with previous use of fertility drugs. Little evidence was found indicating that estrogen- or prolactin-related exposures are associated with an increased risk of lupus. The reduced risk observed among women who had breast fed one or more babies should be examined in other studies. Early natural menopause, rather than decreasing risk of SLE because of reduced estrogen exposure, may be a marker of susceptibility to development of lupus.

N-acetyl Transferase Genotypes in Relation to Risk of Developing Systemic Lupus Erythematosus

The purpose of this study was to examine the association between N-acetyl transferase (NAT) genotypes NAT1 and NAT2 and risk of developing systemic lupus erythematosus (SLE). DNA samples were collected from 243 recently diagnosed cases and 298 controls enrolled in a population-based, case-control study conducted in North Carolina and South Carolina. There was no association between SLE and NAT1 or NAT2 genotypes. We saw some evidence of interaction between the NAT genotypes and use of hair dyes, with higher risk seen among hair dye users who had both the NAT1*10 allele and the NAT2 slow-acetylation genotype. Our results suggest that although

there is little overall association between NAT genotypes and risk of developing SLE, the interaction between NAT1 and NAT2 and specific exposures, such as hair dyes, may be important. This finding highlights the need to consider exposure when assessing genetic susceptibility.

Initiatives

- **Obesity and the Environment** (ES-04-003)
  Obesity and overweight are among the most important health challenges of our time and have reached epidemic proportions in the United States. Obesity in adults, particularly abdominal or upper-body obesity, is associated with increased risk of a number of diseases and metababolic abnormalities, including coronary heart disease, hyperinsulinemia, insulin resistance, type 2 diabetes, certain cancers, and osteoarthritis. The NIEHS is interested in expanding research into two specific areas related to obesity: understanding the role of environmental agents in causing/exacerbating obesity, and developing intervention strategies by improving the built environment and developing sustainable communities. Specific areas of interest include:

  - Examination of the role of *in utero*, neonatal, and prepubertal exposure to environmental agents, particularly environmental estrogens, in the onset or exacerbation of obesity using animal models or human studies.
  - Examination of the effects of lipophilic chemicals stored in adipose tissue on the function and control of fat cells.
  - Examination of the interaction of genetic susceptibility with that of exposures to environmental agents in the etiology of obesity.
  - Development of valid and reliable measures and indicators of sustainable communities (where long-term benefits outweigh potential negative impacts) by multidisciplinary research teams that would promote healthy behaviors and lifestyles to reduce obesity.
  - Examination of the interaction between parameters of the built environment and individual lifestyles, choices, and behaviors that can help delineate factors that can prevent or reduce obesity.
  - Development of new cost-effective interventions that promote healthful environments and behaviors.

- **NIEHS Parkinson's Disease Initiative**
  Spurred by recent scientific findings, there is now an emerging appreciation that Parkinson's disease, like most human diseases, reflects the interaction of genetic susceptibility with environmental exposure(s). What is lacking, however, is a clear mechanistic understanding of the nature of such interactions in disease causation. Such information is essential for developing rational approaches to disease prevention and intervention. To accelerate the pace of progress in this important area and the translation of findings into the public health arena, the NIEHS has created a Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Consortium Program to foster multidisciplinary research approaches to elucidate gene–environment interactions in Parkinson's disease (PD). The ultimate aim of the CCPDER Consortium is to increase the speed with which promising new lines of investigation can be identified and pursued at multiple levels of analysis and for which greater resources can be targeted. It is envisioned that the CCPDER Consortium Program will provide a formal mechanism to strengthen the integrative collaboration among scientists engaged in fundamental laboratory research in PD. This program seeks to provide the science-based foundation for efforts to prevent and/or ameliorate the devastating effects of PD. (Although PD is more prevalent in men, it occurs mostly in later life, thus affecting a large number of women as women constitute a majority of the elderly.) (RFA-ES-02-00)

- **Breast Cancer and the Environment Research Centers**
  The Breast Cancer and the Environment Research Centers program is a network of collaborative research centers comprised of teams including scientists, clinicians, and breast cancer advocates focused on how chemical, physical, and social factors in the environment interact with genetic factors to affect mammary gland development. Jointly supported by the National Institute of Environmental Health Sciences and the National Cancer Institute, this program will span 7 years with annual funding levels of $5 million per year, for a total commitment of $35 million. The centers will study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. Functioning as a consortium of basic scientists, epidemiologists, research translational units, and community advocates within and across centers, Breast Cancer and the Environment Research Centers will investigate mammary gland development in animals and young girls to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. The overall outcomes of the Breast Cancer and the Environment Research Centers are to develop public health messages designed to educate young girls and women who are at high risk of breast cancer about the role(s) of specific environmental stressors in breast cancer and how to reduce exposures to those stressors. These public health messages will be based on the integration of the basic biological, toxicological, and epidemiologic data. (ES-03-001)

Leiomyomata Uteri: Basic Science and Translational Research

The National Institute of Child Health and Human Development (NICHD), the NIEHS, and the NIH Office of Research on Women's Health (ORWH) initiative addresses the need to increase our knowledge and understanding about leiomyomata uteri and the biological processes that lead to their development and long-term sequelae. The general scope of proposed studies could encompass determining the etiology, diagnostic criteria, and underlying pathophysiology deemed important for building a substantive knowledge base. The objective is to strengthen research in this critical area of women's health, contribute to reducing the burden of this disease, and improve the quality of life for women affected with this disorder. Uterine leiomyomata constitute a significant public health concern. While uterine leiomyomata represent the most common gynecologic tumor in women, the mechanisms that initiate uterine leiomyoma growth and pathogenesis are not completely understood. This initiative focuses on basic science and translational research studies that are innovative in their approach to determine the complex molecular basis of this disorder. Results from this research are expected to have important applications for moving advances in basic science research from the laboratory to clinical practice. (HD-03-005)

Centers for Population Health and Health Disparities

In a major initiative to support multidisciplinary research on health disparities, the National Institutes of Health recently created eight Centers for Population Health and Health Disparities (CPHHD). The centers are funded with $60.5 million in grants from the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute on Aging. The purpose of the CPHHD is to support interdisciplinary research leading to an understanding and reduction of health disparities in domestic populations. The eight centers form a network of research teams to explore the complexity of health disparities, following a community-based research approach. Studies focus on obesity, cardiovascular disease, breast cancer, prostate cancer, cervical cancer, mental health, gene-environment interactions, psychosocial stress, and other factors. Investigators follow a community-based research approach with populations including low-income whites, African Americans, Hispanics, and the elderly. (ES-02-009)

*A 2001 report from the Institute of Medicine, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" recommended greater precision in terminology used to reference findings from studies comparing health outcomes in males and females. Accordingly, in the present report, the term "sex difference" is used to refer to biological variables, and the term "gender difference" is used to encompass psychosocial, behavioral, and cultural variables.

Conferences and Workshops

- **Environmental Factors in Autoimmune Disease**
  February 4, 2003
  Durham Marriot at the Civic Center
  Durman, NC

  The purpose of this workshop, which was open to the public, was to explore the role that exposures to environmental agents play in the development and exacerbation of autoimmune diseases.

- **Obesity: Developmental Origins and Environmental Influences**
  2004 Spring Symposium
  Friday, February 20, 2003
  Searle Center, Lecture Hall

- **Genes, Environment, and Disease**
  June 7–9, 2003
  Boston, MS

  The second annual CMGCC symposium, held in connection with the Environmental Genome Project, focused on commonly occurring DNA polymorphisms and their association with environmentally responsive human diseases. By convening a diverse and dynamic group of experts in these fields, we were able to investigate recent trends and new technologies incorporating bioinformatics, genomics, phenomics, and transgenics. Our goal was the optimal design and utilization of mouse models to best represent these human diseases.

- **Symposium on Genetic Variation and Gene Environment Interaction in Human Health and Disease**
  April 16, 2003
  Bethesda, MD

  The National Institute of Environmental Health Sciences (NIEHS), along with the NHGRI and the NIAAA, hosted a half-day satellite symposium, Genetic Variation and Gene Environment Interaction in Human Health and Disease. This symposium provided an opportunity to focus on DNA variation, gene–environment interactions, and their implications for human health and disease. Researchers presenting at the symposium included Drs. Lynn Jorde, Deborah Nickerson, Jeffrey Trent, Charles Rotimi, Clement Furlong, David Crabb, Mary-Claire King, and Martyn Smith.

Health Disparities

- **Uterine Fibroid Growth Study**
  The Fibroid Growth Study (FGS) is designed to investigate why some fibroids grow to become health problems while others do not. Funding is provided jointly by the NIEHS and the National Center for Research on Minority Health and Health Disparities.

- **Work and Health Disparities among Rural Women**
  For more than 20 years, women in northeastern North Carolina have been organizing to address social, economic, and health issues arising from industrial work in an area with few employment opportunities. Although the impacts of racial discrimination and fast-paced assembly-line production have been described by government inspectors, journalists, and women advocating on their own behalf, research has not quantified the occurrence of specific health outcomes or risk factors for adverse outcomes. Through a collaborative project linking investigators at Duke University, the University of North Carolina, and the Center for Women's Economic Alternatives, we proposed to evaluate occupational roots of health disparities among women in a five-county region of northeastern North Carolina.

- **Social and Physical Environments and Health Disparities Project**
  Social inequalities have been linked to health disparities at the individual and the population levels and are associated with income inequalities, not simply with absolute income. There is clear evidence of a strong association between socioeconomic status (SES), economic development, and cardiovascular disease (CVD), the largest contributor to all-cause mortality in the United States. The pathways linking these social and economic inequalities to health are not yet well understood. The Social and Physical Environments and Health Disparities Project is a community-based participatory research partnership between the University of Michigan School of Public

Health, community-based organizations, and health care institutions in Detroit. The specific aims of the proposed project are to: 1) estimate the relationship between racial and ethnic group status, SES, and mental and physical health in a stratified, multistage probability sample (n = 1000) of an adult population in Detroit, MI; and estimate the relationship between racial or ethnic group status, SES, and specific biomarkers for cardiovascular risk factors in a subset of this sample (n = 200); 2) examine the relationships between neighborhood sociodemographic context (e.g., concentrated poverty), selected aspects of the physical environment (exposure to PM10 and PM2.5), and selected aspects of the social environment (e.g., acute life events); 3) investigate independent and cumulative effects of exposure to psychosocial stressors on biological risk markers for CVD (e.g., total serum cholesterol and LDL); 4) document the strength of the association between airborne particulate matter and selected proximate risk and protective factors (e.g., elevated plasma homocysteine, F2 isoprostane) for CVD; 5) investigate potential mediating and moderating effects of behavioral and psychosocial responses to stressors (e.g., smoking), and micronutrient intake (e.g., intake of folic acid, B-6, and B-12) on the relationships between selected aspects of the physical and social environments and biological markers for CVD, and self-reported CVD and depression; and 6) create a Community Outreach and Education Program to disseminate and translate knowledge gained from the study to inform new and established intervention and policy efforts in Detroit.

- **Systemic Lupus Erythematosus: The Carolina Lupus Study**

  Systemic lupus erythematosus (SLE) is an autoimmune disease that can cause severe damage to the kidneys, joints, and other tissues. Ninety percent of SLE patients are women, and compared to whites, African Americans are three to four times more likely to develop the disease. Mortality is also higher among Black, compared to white, SLE patients. Reasons for the African American excess risk are not known. The NIEHS and the National Center on Minority Health and Health Disparities (NCMHD) have joined to create the Carolina Lupus Study, a population-based, case-control study in eastern North Carolina and South Carolina designed to examine hormonal and environmental influences on the etiology of SLE. This study offers the opportunity to examine hormonal, occupational, and environmental risk factors in a previously understudied population. These efforts may help illuminate etiologic pathways and develop prevention strategies for susceptible populations. The study participants are 90 percent women and 55 percent African American. Environmental exposures under study include silica dust, solvents, heavy metals, and pesticides. The influence of genetic susceptibility to disease risk will also be assessed.

- **Uterine Fibroid Study**

  Uterine fibroids are the leading indication for hysterectomy among pre-menopausal women in the United States. Based on hysterectomy statistics, African American women appear to be at three- to ninefold higher risk than white women, although it is not done if this disparity reflects a true difference in incidence or prevalence of uterine fibroids or, instead, is due to differences in diagnosis and treatment. To better define the cause of this health disparity, the NIEHS and the ORMH have initiated a study of uterine fibroids among 35- to 49-year-old members of a large prepaid health plan in Washington, DC. After 1 year of data collection, 285 Black and 123 white women have been enrolled. Data from ultrasound examinations have been completed for 226 Black women and 167 white women. In this group, 73 percent of Black women had uterine fibroids, compared to 48 percent of white women. These data indicate that the differences in hysterectomy rates are not just a result of diagnostic/treatment bias. There are real differences in uterine fibroid risk between blacks and whites and the NIEHS hopes to help define some of the environmental triggers for uterine fibroid development.

- **Breast Cancer**
  African American women appear to be at greater risk of developing more aggressive forms of breast cancer and are more likely to die from this disease than are white breast cancer victims. The reasons will most likely prove to be multifactorial, but environmental exposures might play a role. A recently published study supported by the NIEHS showed that women with higher blood levels of the organochlorine pesticide, dieldrin, had twice the risk of later breast cancer development than did women with low levels of this pesticide. Since many people of color engage in farm work, they and their families would be expected to have higher exposures to endocrine-disrupting compounds, such as dieldrin, and consequently, would be at higher risk for breast cancer development. The NIEHS, in partnership with the NCI, has a long-term Agricultural Health Study of farmers and pesticide applicators, as well as their spouses and children, to determine the health consequences of exposures typical in rural environments. The NIEHS was particularly instrumental in ensuring that a large part of this cohort included African American families.

National Institute of General Medical Sciences

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training for the basic biomedical sciences. The NIGMS supports research on cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus. This knowledge is necessary in order to understand the disease process. Most studies supported by the NIGMS do not target any particular disease or condition, but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, and genetics. Often basic research supported by the institute will result in findings pertinent to women's health. Notable recent examples of such project are:

- Several NIGMS investigators study the metabolic enzymes that control estrogen levels. Dr. Virginia Cornish is attempting to evolve a protein receptor for estrogen that can be used in diagnostics. Dr. David Flockhart studies the effect of metabolism on estrogen antagonist therapy, and Dr. Mary Vore is looking at drug metabolism in pregnancy and the effects of estrogens on transporter control.

- Dr. Steven Rosen reported (*Science*, 2003) extending his pioneering work on L-selectins to demonstrate their presence on trophoblast cells of the blastocyst. He and his colleagues described the role of L selectins in delivering and binding the blastocyst to the uterine wall. Some unexplained cases of infertility and early pregnancy loss may be due to failure of the trophoblast to properly attach to the uterine wall. Understanding the molecular processes leading up to implantation may provide information useful for treating infertility

- Dr. Gongyi Zhang (*Nature*, 2003) determined how Tall-1, a protein which causes B cells to mature and produce antibodies, binds to its main receptor, Baff-R. Lupus is an autoimmune disease that affects predominantly women. Individuals with lupus have high levels of Tall-1 in their blood. Dr. Zhang's structural studies are being used to develop a Baff-R fragment, containing one of two binding domains for Tall-1, as a drug. The drug would block Baff-R binding to Tall-1 and thus prevent it from triggering the B cell maturation that seems to contribute to lupus.

The NIGMS also supports research in drug discovery, synthetic chemistry, and pharmacology, including studies in proteomics, glycomics, pharmacogenetics, and pharmacogenomics. These studies often have broad applicability to a wide variety of diseases or organ systems, including those specific to, or which disproportionately affect, women. For example, natural plant and animal products are a major source of bioactive agents. One such agent is taxol, which is derived from the bark of the yew tree. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. While very promising in the treatment of ovarian and breast cancer,

only limited natural supplies of taxol were available. Improved approaches for isolation, purification, and synthesis have enabled widespread clinical trials of taxol. Unfortunately, taxol treatment while effective is often accompanied by severe side effects. Second-generation taxoids developed by NIGMS-supported investigator Dr. Iwao Ojima have distinct advantages over the parent drug in that they have outstanding oral bioavailability, have been found to be at least as active as the approved drugs when tested in human carcinoma cell lines and, most significantly, retain their activity against drug-resistant human carcinoma cells. Studies of second-generation taxoids continue to hold promise for improved efficacy, with fewer side effects.

Interindividual drug responses depend on genetic variation as well as modifying factors, such as environment, diet, other medications, age, and gender. Under Program Announcement (PA) Mechanisms Underlying Individual Variations in Drug Response (PA-99-016), the NIGMS supports investigations of critical candidate proteins and genes that may contribute to pharmacogenetic/pharmacogenomic variations in drug metabolism and clearance. In addition, applications received in response to a Request for Applications (RFA) Pharmacogenetic Research Network and Database (RFA-GM-99-004), the NIGMS has built on this by supporting the formation of a coordinated Pharmacogenetic Research Network and Database. Dr. David Flockhart, M.D., Ph.D., director of the Division of Clinical Pharmacology at the Indiana University School of Medicine and a member of the NIGMS Pharmacogenetic Research Network, recently demonstrated that the effectiveness of tamoxifen therapy for the treatment and prevention of breast cancer may be limited by the use of drugs commonly prescribed to prevent the side effects associated with tamoxifen treatment. His study in the *Journal of the National Cancer Institute* (December, 2003) suggests that metabolism of tamoxifen may be modified by the genetic makeup of the person taking the drug. In addition, he demonstrated that the antidepressants paroxetine and fluoxetine (normally prescribed to counter hot flashes, a side effect of tamoxifen therapy) inhibit the enzyme that breaks down tamoxifen into its most active metabolite, 4-hydroxy-tamoxifen. Genetic variations in metabolism of tamoxifen may account for differences in effectiveness of the therapy between patients.

The NIGMS extensively supports interdisciplinary research training of predoctoral and postdoctoral scientists, and the Medical Scientist Training Program (MSTP) provides training of students with both a medical and scientific background. These future scientists, with both M.D. and Ph.D. degrees, will be ideally poised to address research problems in cell biology, biochemistry, immunology, biophysics, molecular biology, and genetics, and to relate their results to clinical areas. The predoctoral training program in cell biology, molecular biology, and biochemistry encompasses research training on cellular mechanisms, enzymology, and molecular mechanisms relevant to understanding cell growth, activation, division, and motility. The genetics training program at the predoctoral level prepares future scientists to understand the genetic mechanisms operant in the inheritance of genetic factors, transcriptional control, mutagenesis, DNA structure, recombination and repair, and the role of genes in cell division and differentiation. Postdoctoral training programs in genetics foster the development of M.D.s and Ph.D.s with expertise in genetic approaches to disease. The training program in molecular biophysics focuses on the development of scientists able to determine the three-dimensional structures of biologically active molecules and the relationship of the structure to function. These future structural biologists will be in a position to rationally design drugs to treat diseases, such as breast cancer. The NIGMS training program, aimed at the chemistry/biology interface, has the goal of fostering more chemists with a knowledge and understanding of biological systems. This is an area that also will be critical for the design of new drugs, and diagnostic and preventive approaches. This program complements the existing training program in the pharmacological sciences that prepares young scientists to investigate the biochemical systems that are amenable to pharmacological intervention and to investigate the pharmacology of drug action and drug toxicity.

A basic understanding of the etiology of a disease, the predisposing factors, the cellular processes involved, and the mechanisms that

promote disease progression are necessary for prevention, early diagnosis, and effective treatment of the disease. The National Institute of General Medical Sciences' support of fundamental research impacts on virtually all these areas. In addition, the NIGMS supports interdisciplinary research training at the predoctoral and postdoctoral levels, providing the personnel for biomedical research. Specific efforts on the part of NIGMS in pharmacogenetics addressing interindividual drug responses as they are influenced by genetic variation, as well as modifying factors such as environment, diet, age, and gender, as well as other institute programs, can be found on the NIGMS homepage (*http://www.nigms.nih.gov*).

National Institute of Mental Health

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders than boys. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. There are also differences in the course and severity of mental disorders between men and women. For example, men have an earlier average age of onset of schizophrenia, while women are more likely to suffer from the rapid-cycling form of bipolar disorder. Additionally, women are at increased risk of recurrence of depression during certain times of reproductive change, such as in the perinatal period.

The World Health Organization's study, the Global Burden of Disease, provided a measure of lost years of healthy life due to premature death, as well as years lived with disability. For the first time, the burden of illnesses was shifted from an almost exclusive focus on premature mortality to one that included chronic illness. The study enabled a comparison of the burden of different illnesses. Based on 1990 data, depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder were among the top ten conditions accounting for years lived with disability in women. This public health burden stems from three aspects of the epidemiology of the disorders. First, these conditions are highly prevalent. For example, in a 1-year period, an estimated 12 percent of women meet criteria for depression and approximately the same percentage meet criteria for an anxiety disorder. Second, all four of the most disabling mental disorders have an early onset and a recurrent or chronic course. Third, since these disorders rise markedly in incidence in adolescence and peak in incidence in young to middle adulthood, they can adversely impact educational and occupational attainment as well as social and interpersonal functioning. The study did not consider the impact of maternal mental illness on children in assessing disability burden, but in other numerous studies, maternal mental illness has been associated with poorer child functioning. Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender differences in mental health and mental illness. Through crosscutting programs, such as the Women's Mental Health Research Team, NIMH has fostered interdisciplinary collaboration and the translation of basic findings into applications to improve diagnosis, treatment, services, and prevention. This 2003-2004 NIMH report highlights findings from areas of basic and clinical neuroscience, epidemiology and risk factors, and intervention development.

Research highlights in these areas are grouped by five major subheadings: 1) developmental aspects of sex and gender* differences; 2) mood and anxiety disorders; 3) eating disorders; 4) schizophrenia and other serious mental disorders; and 5) health behavior, AIDS, and mental health disparities. A section on Other Program Activities describes the Women's Mental Health Program and Team, NIMH-sponsored meetings, and research

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funding mechanisms relevant to women's mental health and sex and gender differences research.

Developmental Aspects of Sex and Gender Differences

Many mental disorders have striking gender disparities in prevalence, as shown in population-based epidemiology studies of U.S. adults. Such disparities often have their origins earlier in the lifespan. Depression, anxiety, and eating disorders are three conditions for which the incidence increases sharply around puberty. In other conditions, such as attention deficit disorder and autism, gender disparities are manifest in children, often from early childhood on. Sex differences can be due to a variety of factors, including the effects of sex-linked genes, sex hormones, and differences in environmental stressors that impact brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental illnesses.

Sex Differences in Emotional Processing

Activity in a Brain Region Involved in the Processing of Emotional Information Shows Sex Differences

The amygdala is a part of the brain that is known to be involved in the processing of emotional information and in the modulation of memory storage of emotionally charged information. In this NIMH-supported research, investigators show distinct sex differences in the activation of this brain region. Specifically, in men activation of the right amygdala shows a stronger correlation with memory of emotionally arousing information, whereas in women it is the activation of the left amygdala that shows the stronger correlation. This study, and others from the same laboratory, reinforces the concept that the neural mechanisms underlying the processing of emotionally arousing information involve significant sex differences. Understanding these basic phenomena and how they differ between men and women is especially important in developing a better understanding of mood disorders.

(Cahill, L., Uncapher, M., Kilpatrick, L., Akire, M.T., and Turner, J. (2004) Sex-related hemispheric lateralization of amygdala function in emotionally influenced memory: An fMRI investigation. *Learning and Memory*, 11, 261-66.)

Specific Neural Systems Are Shown to be Involved in the Up- and Downregulation of Emotion

The interaction of cognition and emotion is a critically important question as scientists grapple with understanding the basis of mood disorders and how to develop and refine effective therapies for these disorders. While the amygdala, a region of the brain buried in the temporal lobe, is well understood to be involved in the processing of emotional information, it is clear that the amygdala exerts its influence in the context of a complex set of interactions among multiple brain systems. In the present study, NIMH-supported investigators studied a group of women subjects as they up- or downregulated their emotional (negative) reaction to a series of aversive pictures. The results suggest that specific regions of the prefrontal cortex show a highly correlated pattern of activation in association with the amygdala as subjects attempt to modulate their reaction to aversive pictures. The ability to reappraise emotionally charged situations is critical to behavioral therapies (e.g., cognitive behavior therapy) aimed at dealing with a variety of mental disorders. (Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., and Gross, J.J. (2004). For better or for worse: Neural systems supporting the cognitive down- and upregulation of negative emotion. *Neuroimage*, 23(2), 483-99.)

Hormones Modulate Maternal Aggression in Mice

An important system known to modulate the stress response involves the hypothalamus, the pituitary, and the adrenal glands, together referred to as the "HPA axis." The hormone corticotrophin releasing factor (CRF) is an important regulator of the HPA axis activity. It is well established that lactating female mice exhibit a very aggressive response as they protect their nest from potential intruders. In the present study, NIMH-supported investigators tested

whether decreasing CRF levels in lactating mice would alter the level of maternal aggression they exhibited. They found a complex set of results—increasing levels of CRF in the mouse inhibited maternal aggression, but artificially decreasing CRF levels had no effect on aggression. These findings do support a role for CRF in maternal aggression but additional work is needed to fully understand its role. Better understanding of the functioning of the HPA axis and how it differs between the sexes is very important in understanding the development of a variety of mental disorders, especially mood disorders.
(Gammie, S.C., Negron, A., Newman, S.M., and Rhodes, J.S. (2004). Corticotropin-releasing factor inhibits maternal aggression in mice. *Behavioral Neuroscience*, 118(4), 805-14.)

Perinatal Effects on Development and Behavior

Maternal Behavior Programs Gene Regulatory Components

Studies revealed a novel mechanism through which early environmental exposure can impact long-term changes in gene expression impacting stress responsiveness. Increased grooming by rat mothers altered the offspring epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus. Offspring of mothers that showed high levels of grooming were found to have differences in DNA methylation (which determines gene activity) as compared to offspring of low grooming mothers. These differences emerged over the first week of life, were reversed with cross fostering, persisted into adulthood, and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter. Central infusion of a histone deacetylase inhibitor reversed effects of maternal care on GR gene regulatory components, suggesting a causal relation among epigenomic state, GR expression, and the maternal effect on stress responses in the offspring. These data demonstrate how an early experience can affect the expression of a gene coding for part of the brain stress response system through effects on DNA binding elements and alterations in gene regulatory components.
(Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., and Meaney, M.J. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004 Aug;7(8):847-54.)

Altered Prenatal Hormone Environment May Contribute To Increased Risk of Tic Disorders and Obsessive Compulsive Disorder

Sex hormones, specifically androgens, are known to contribute to the sexual differentiation process prenatally. In this NIMH-supported research, the link between this process and the risk for increased prevalence of tic disorders (e.g., Tourette's syndrome) was explored by studying both children and adults of both sexes. Consistent with the author's hypothesis, the presence of a tic disorder in women was associated with increased masculine play preferences, a more typically "masculine" performance pattern on spatial tasks known to differentiate between the sexes, and what is termed "gender dysphoria"—general confusion or discomfort with a person's birth gender.
(Alexander, G.M. and Peterson, B.S. (2004). Testing the prenatal hormone hypothesis of tic-related disorders: Gender identity and gender role behavior. *Development and Psychopathology*, 16, 407-20.)

Prenatal Hormone Environment and the Development of Typical Patterns of Behavior towards Infants

Rhesus monkeys display a sex difference in their interest and interaction with infants, with females displaying a greater interest than males in infants. In the present study, NIMH-supported researchers sought to discover whether the presence of sex hormones in the prenatal environment affected subsequent sex-typical patterns of interaction with infants. They were specifically interested in understanding whether prenatal androgen was a significant influence on expression of this behavior. While the authors demonstrated strong sex differences between male and female monkeys in their interactions with infant monkeys, they failed to demonstrate that prenatal androgens contributed to this effect. This demonstrates the complex nature of interactions between the prenatal environment and specific non-hormonal, perhaps social, influences on sex-typical behaviors and further underscores the need for additional research in this area.

(Herman, R.A., Measday, M.A., and Wallen, K. (2003) Sex differences in the interest in infants in juvenile rhesus monkeys: relationship to prenatal androgen. *Hormones and Behavior*, 43(5), 573-83.)

Prenatal Influenza May Play a Role in the Etiology of Schizophrenia

Some, but not all, previous studies suggest that prenatal influenza exposure increases the risk of schizophrenia. These studies used dates of influenza epidemics and maternal recall of infection to define influenza exposure, suggesting that discrepant findings may have resulted from exposure misclassification. In order to examine this question, the investigators performed a nested case-control study of a large birth cohort, born from 1959 to 1966, and followed up for psychiatric disorders 30 to 38 years later. They compared 64 birth cohort members with schizophrenia spectrum disorders to 125 members of the cohort without schizophrenia and examined the role of maternal influenza antibodies with risk of schizophrenia. The authors found that the risk of schizophrenia was increased sevenfold for influenza exposure during the first trimester. If confirmed, the results may have implications for the prevention of schizophrenia and for unraveling pathogenic mechanisms of the disorder. (Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., Babulas, V.P., and Susser, E.S. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61:774-80.)

Defining the Neural Basis of Sexual Behavior

NIMH-sponsored investigators have identified a molecular pathway through which reproductive hormones influence sexually dimorphic development of specific brain regions and related adult reproductive behaviors in rodents. In particular, a hormone-mediated increase in an inflammation-related protein, prostaglandinE2 (PGE2), during development results in the masculinization of brain and behavior. Perinatal exposure to common medications, such as aspirin and related compounds, results in impaired sexual behavior in adult males. Conversely, increasing PGE2 in young females results in increased display of male reproductive behavior. Alterations in neuronal development were observed only in sexually dimorphic brain regions, but not in areas related to learning and memory. This significant finding indicates that certain prostaglandin-mediated signaling represents a key cellular mechanism for sexual differentiation of both brain and behavior, and suggests close examination of the use of certain pain relievers during pregnancy. (Amateau, S.K. and McCarthy, M.M. (2004). Induction of PGE2 by estradiol mediates development of masculinization of sex behavior. *Nature Neuroscience* 7:643-50.)

Sex Differences in Brain and Cognition

GENDER DIFFERENCES IN THE BRAIN INFLUENCED BY CELL DEATH

Certain mental illnesses, such as ADHD and depression, affect males and females differently and are more prevalent in or may display different symptoms in one sex than the other. These gender differences may be explained by sexual dimorphism—a physical distinction between the sexes, which is also observed in the brain. The establishment of male or female characteristics in the brain is directed, in part, by the influence of reproductive hormones on cell survival during development. The developing brain generates a surplus of cells, but once the brain is wired, surplus cells and faulty connections are eliminated by a process called programmed cell death. Recent studies by NIMH grantees suggest that a protein called Bax, which is involved in programmed cell death, controls developmental events that establish sexual dimorphism in specific areas in the mouse forebrain. Normally, one area (AVPV) contains more neurons in females; another (BNSTp) has more neurons in males. The researchers discovered that eliminating, or "knocking-out," the Bax gene abolished these sex differences in neuron number. These results suggest that deletion of the Bax gene rescued neurons that would have otherwise been eliminated by programmed cell death as the brain matured. Importantly, the effects of Bax deletion were observed in animals with normal levels of reproductive hormones, suggesting that these hormones work through Bax to modulate neuronal death during normal brain development. However, the absence of Bax did not eliminate all sexual dimorphism in the brain, suggesting that additional proteins

or mechanisms may establish certain aspects of sex-specific brain development. These studies will increase our understanding of sex differences in the brain that may confer susceptibility to mental disorders and also facilitate the development of improved therapies.
(Forger, N.G., Rosen, G.J., Waters, E.M., Jacob, D., Simerly, R.B., and deVries, G.J. Deletion of bax eliminates sex differences in the mouse forebrain. *Proc Natl Acad Sci USA* 101:13666-71, 2004.)

Neuroprotective Effects of Estrogen in Brain

Estrogen receptor (ER) activation has been shown to protect neurons in a number of different studies. However, it is unclear what the roles of the different types of estrogen receptor (ER alpha and ER beta) are in neuroprotection. To address this question, the investigators examined the impact of selective ER agonists for either ER alpha or ER beta to prevent the death of hippocampal neurons exposed to a toxin. Results indicated that both receptor subtypes could be involved in estrogen neuroprotection. As ER beta is highly expressed in the brain and has little or no expression in the breast or uterus, discovery and design of ER beta selective molecules could provide a strategy for activating the beneficial effects of estrogen in the brain without activating untoward effects of estrogen in reproductive organs.
(Zhao, L., Wu, T.W., and Brinton, R.D. Estrogen receptor subtypes alpha and beta contribute to neuroprotection and increased Bcl-2 expression in primary hippocampal neurons. *Brain Res*. 2004 Jun 4;1010(1-2):22-34.)

Estrogen Modifies Neuronal Structure through Novel Mechanisms

Estrogen treatment induces branching of neurons in the hippocampus (an area of the brain involved in memory formation) of the rat. Results of this study showed that estrogen treatment of mice caused an increase in neuronal spine processes and molecular markers of increased neuronal synaptic communication within a subset of neurons of the hippocampus. These structural changes were associated with improved performance on a spatial episodic memory task. Taken together, the results suggest a previously uncharacterized role for estrogen in altering neuronal communication that is associated with enhancement of hippocampal-dependent memory.
(Li, C., Brake, W.G., Romeo, R.D., Dunlop, J.C., Gordon, M., Buzescu, R., Magarinos, A.M., Allen, P.B., Greengard, P., Luine, V., and McEwen, B.S. Estrogen alters hippocampal dendritic spine shape and enhances synaptic protein immunoreactivity and spatial memory in female mice. *Proc Natl Acad Sci U S A*. 2004 Feb 17;101(7):2185-90.)
(Akama, K.T. and McEwen, B.S. Estrogen stimulates postsynaptic density-95 rapid protein synthesis via the Akt/protein kinase B pathway. *J Neurosci*. 2003 Mar 15;23(6):2333-9.)

Mood and Anxiety Disorders

Mood and anxiety disorders are the most highly prevalent of the mental disorders. By early adolescence, gender differences in the incidence of major depression and anxiety disorders are evident. Genetic and hormonal factors, sex differences in stress response, and risk factor exposures have all been implicated in gender disparities in these disorders. Although the mood and anxiety disorders are clinically distinct, they often co-occur and are thought to share some etiological factors.

Mood and anxiety disorders often result in significant functional impairment, decreased health-related quality of life, lost work productivity, and even hospitalization and suicide. In a landmark study of The Global Burden of Disease, funded by the World Bank and the World Health Organization, major depression led a list of medical conditions in accounting for years of productive life lost to functional disability in women; and this depression-related disability is projected to increase over the next two decades. There is substantial evidence that undiagnosed, untreated mood and anxiety disorders adversely affect the course of general medical conditions and may even predispose to them.

The NIMH funds a wide range of basic and clinical research to enhance understanding of the mood and anxiety disorders. In order to reduce the functional impact of these illnesses, the NIMH also seeks to translate basic and clinical findings into the more applied realm of intervention development, refinement, and improvement. Below is a sample of the NIMH

2003 and 2004 research highlights from studies of mood and anxiety disorders.

Basic and Clinical Neuroscience

ESTROGEN RECEPTORS INTERACT WITH ADRENAL STRESS RESPONSE SYSTEM

While the estrogen receptor alpha is believed to play a role in the regulation of sexual behavior, the function of the estrogen receptor beta (ER beta) in brain is largely unknown. ER beta is localized in an area of the brain (the paraventricular nucleus or PVN) that is involved in the regulation of stress hormone release. Results of this study showed that inhibition of the ER beta receptors reduced stress hormone release in female rats. This effect was only observed during the portion of the rat estrus cycle when endogenous estradiol was lower. In contrast, upregulation of ER beta expression in the PVN by the stress hormone corticosterone was demonstrated for the portion of the estruscycle during which estradiol is high, suggesting to the authors that stress hormones modulate ER beta expression when it is already activated to an optimal level by endogenous estradiol. These data suggest that ER beta in the PVN may modulate the hypothalamic pituitary axis response to stress in a manner that is sensitive to ongoing stress hormone secretion. (Isgor, C., Cecchi, M., Kabbaj, M., Akil, H., and Watson, S.J. Estrogen receptor beta in the paraventricular nucleus of hypothalamus regulates the neuroendocrine response to stress and is regulated by corticosterone. *Neuroscience*. 2003;121(4):837-45.)

ESTROGEN MEDIATES SEX DIFFERENCES IN STRESS-INDUCED PREFRONTAL CORTEX DYSFUNCTION

Many anxiety disorders, as well as major depressive disorder (MDD), are at least twice as prevalent in women as in men, but the neurobiological basis of this discrepancy has not been well studied. MDD is often precipitated by exposure to uncontrollable stress, and is frequently characterized by abnormal or disrupted prefrontal cortex (PFC) function. In animals, exposure to stress has been shown to cause PFC dysfunction, but sex differences in this effect have not been investigated. This study tested male and female rats on a PFC-dependent working memory task after administration of a drug that activates stress systems in the brain. Female rats were impaired by lower drug doses than males during proestrus (high estrogen), but not during estrus (low estrogen). Similarly, ovariectomized females showed increased stress sensitivity only after estrogen replacement. These results suggest that estrogen amplifies the stress response in PFC, which may increase susceptibility to stress-related disorders. (Shansky, R.M., Glavis-Bloom, C., Lerman, D., McRae, P., Benson, C., Miller, K., Cosand, L., Horvath, T.L., and Arnsten, A.F. Estrogen mediates sex differences in stress-induced prefrontal cortex dysfunction. *Mol Psychiatry*. 2004 May;9(5):531-8.)

A PROGESTERONE METABOLITE HAS ANTIDEPRESSANT EFFECTS

A metabolite of progesterone, 3a,5a-THP, may mediate this hormone's effects to reduce depressive behavior of female rats in part through actions on a part of the brain known as the hippocampus. Results of this study showed that pregnant rats had higher plasma and hippocampal 3a,5a-THP levels and less depressive behavior (decreased immobility, increased struggling, and swimming) in the forced swim test than did postpartum rats. In contrast, administration of a compound that decreased 3a,5a-THP levels in plasma and hippocampus increased indices of depressive behavior in rats. Together, these data suggest that 3a,5a-THP in the hippocampus may mediate aspects of antidepressive behavior of female rats. (Frye, C.A. and Walf, A.A. Hippocampal 3alpha,5alpha-THP may alter depressive behavior of pregnant and lactating rats. *Pharmacol Biochem Behav*. 2004 Jul;78(3): 531-40.)

ESTROGEN RECEPTOR BETA SELECTIVE SERMS HAVE ANTIDEPRESSANT ACTION IN PRECLINICAL TEST

This study examined the actions of selective estrogen receptor modulators (SERMs) with different affinities for the intracellular estrogen receptor (ER) alpha or beta isoforms in a rodent behavioral test used to screen for antidepressant activity. Data from these studies suggest that estrogenic antidepressive effects may involve actions at ER beta. (Walf, A.A., Rhodes, M.E., and Frye, C.A. Antidepressant effects of ERbeta-selective

estrogen receptor modulators in the forced swim test. *Pharmacol Biochem Behav*. 2004 Jul;78(3):523-9.)

ESTROGEN TREATMENT INCREASES SEROTONIN 2A RECEPTORS IN POSTMENOPAUSAL WOMEN

In animal models, estrogen has been shown to influence serotonin receptors. Modulation of serotonin may be one way that estrogen affects mood and cognition. In this study, investigators examined the effect of estrogen on brain serotonin 2A receptors through the use of positron emission tomography (PET) scans in postmenopausal women to see whether there was any correlation of receptor changes with cognition and mood. Serotonin receptor binding was significantly increased after estrogen replacement in prefrontal areas of the brain. Verbal fluency and Trail Making Test performance, but not mood, were significantly improved by estrogen without correlation with receptor changes. (Kugaya, A., Epperson, C.N., Zoghbi, S., van Dyck, C.H., Hou, Y., Fujita, M., Staley, J.K., Garg, P.K., Seibyl, J.P., and Innis, R.B. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. *Am J Psychiatry*. 2003 Aug; 160(8):1522-4.)

Sex Differences and Hormonal Influences on Mood and Anxiety Disorders

Hormone Replacement Therapy and Antidepressant Effects in Peri- and Postmenopausal Depression

NIMH-funded researchers evaluated the effects of hormone replacement therapy (HRT) alone and in combination with the antidepressant, fluoxetine, on mood, cognition, sleep, and endocrine parameters in peri- and postmenopausal women. Plasma hormone levels were assessed in peri- and postmenopausal depressed patients and postmenopausal normal control women before and after 8 weeks of treatment with estrogen alone or estrogen plus progesterone or with estrogen combined with antidepressant medication. Menopausal depressed women reported greater severity of hot flashes, and poor sleep compared with control women. In menopausal depressed women, estradiol did not enhance the effect of antidepressant alone on mood ratings. These findings differ from other reports in the literature, and may be due to differences in the severity of major depressive episodes, or the dose and preparation of hormone therapy. Further work is needed to understand the interaction of hormone therapy and antidepressant drug treatment on mood. (Parry, B.L., Meliska, C.J., Martinez, L.F., Basavaraj, N., Zirpoli, G.G., Sorenson, D., Maurer, E.L., Lopez, A., Markova, K., Gamst, A., Wolfson, T., Hauger, R., and Kripke, D.F. Menopause: Neuroendocrine changes and hormone replacement therapy. *J Am Med Womens Assoc*. 2004, 59:135-45.)

Relationship between Menopausal Hormone Status and Depression

Mood and reproductive function were prospectively evaluated in asymptomatic premenopausal women to determine whether the onset of depression was temporally linked to the perimenopause. Women followed through the onset of menopause, with both hormonal and mood measures, showed an increased risk of depression during the 24 months surrounding the final menses, indicating that the late perimenopause may be a time of increased susceptibility to develop depression in some women. In a separate study, researchers examining the role of ovarian function and mood during the perimenopause, found that when ovarian function increased (demonstrated by higher lower levels of FSH) that mood improved in women with perimenopausal depression. (Schmidt, P.J., Haq, N., and Rubinow, D.R. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry*. 2004 Dec;161(12):2238-44.) (Daly, R.C., Danaceau, M.A., Rubinow, D.R., and Schmidt, P.J. Concordant restoration of ovarian function and mood in perimenopausal depression. *Am J Psychiatry*. 2003 Oct;160(10):1842-6.)

Relapse of Depression during Pregnancy Common following Antidepressant Discontinuation

Pregnancy has frequently been referred to as a time of emotional well-being for patients. However, systematic data about the risk for relapse of depression during pregnancy are sparse. Investigators prospectively followed

women with a history of depression who were asymptomatic at the time of conception and who had discontinued antidepressant therapy. Seventy-five percent of women relapsed during pregnancy, most during the first trimester. Relapse was more common in those women with histories of chronic depression. Pregnancy was not "protective" with respect to risk for relapse of depression. Careful treatment planning is necessary for those women on antidepressants who plan to conceive or who become pregnant. (Cohen, L.S., Nonacs, R.M., Bailey, J.W., Viguera, A.C., Reminick, A.M., Altshuler, L.L., Stowe, Z.N., and Faraone, S.V. Relapse of depression during pregnancy following antidepressant discontinuation: A preliminary prospective study. *Arch Women Ment Health*. 2004 Oct;7(4):217-21.)

The Hidden Epidemic of Eepression in New Mothers

As many as 10 percent of all new mothers suffer from postpartum depression. However, it frequently goes undetected in the typical 4 to 6 week obstetrical follow-up visit. Recognizing this failure, a large pediatric primary care practice offered all new mothers a short questionnaire at each well-child visit during the child's first year, beginning with the 2-week visit. Approximately half of all mothers completed the screening, with 27 percent of these reporting high levels of depressive symptoms. Mental health referrals increased significantly after the initiation of the screening procedure suggesting that well-child visits offer a favorable setting for the detection of postpartum depression. Treating depression in new mothers, however, poses the dilemma of exposing nursing infants to antidepressant drugs. NIMH researchers, therefore, developed a simple assay system to measure the breast milk concentrations of the 12 most commonly prescribed antidepressants (including the SSRIs and tricyclics). The simple, routine methodology they designed allows one technician to process 30 breast milk specimens a day and will allow researchers to develop the data required to set clinical guidelines regarding the exposure for infants of breastfeeding mothers who are being treated with antidepressant medications during the postpartum period.
(Chaudron, L.H., Szilagyi, P.G., Kitzman, H.J., Wadkins, H.I., and Conwell, Y. Detection of postpartum depressive symptoms by screening at well-child visits. *Pediatrics*. 2004, 113:551-8.)
(Hostetter, A.L., Stowe, Z.N., Cox, M., and Ritchie, J.C. A novel system for the determination of antidepressant concentrations in human breast milk. *Ther Drug Monitoring*. 2004, 26:47-52.)

Women with PTSD More Likely to Have Other Health Problems

Post-traumatic stress disorder (PTSD) is associated with high numbers of self-reported physical symptoms and functional disability in clinical samples. In order to assess these associations in population samples using actual physician-coded diagnoses, researchers surveyed 1,225 female HMO enrollees randomly selected from the current membership of a large, staff model HMO. Using the PTSD Checklist they compared women with low, moderate, and high scores with respect to differences in self-reported physical health status, functional disability, numbers and types of self-reported health risk behaviors, common physical symptoms, and physician-coded ICD-9 diagnoses. Compared to women with low PTSD symptom severity, those with moderate or high severity reported significantly higher functional disability, rates of abuse and neglect, health risk behavior scores, as well as higher mean numbers of common physical symptoms. Compared to women with low PTSD symptom severity those with moderate or high severity had significantly higher adjusted odds ratios for aversive physical symptoms. The mean number of physician-coded ICD-9 diagnoses was also significantly higher in both the moderate and high severity groups. Among female HMO members, PTSD symptoms are associated with a wide range of both self-reported and physician-coded adverse physical health outcomes.
(Ciechanowski, P.S., Walker, E.A., Russo, J.E., Newman, E., and Katon, W.J. Adult health status of women HMO members with post-traumatic stress disorder symptoms. *Gen Hosp Psychiatry*. 2004 Jul-Aug;26(4):261-8.)

Eating Disorders

Eating disorders affect eight to ten times more females than males, with symptoms commonly presenting in adolescence and persisting into

adulthood. The most common forms of eating disorders are anorexia nervosa (self starvation) and bulimia nervosa (binge eating and purging). Anorexia nervosa occurs in approximately 0.5 to 1 percent of young women. Bulimia nervosa affects 1 to 3 percent of adolescent girls and young women. In addition to evidence for social risk factors, there is also evidence of biological vulnerabilities in relation to eating disorders. Although they are less common than depressive and anxiety disorders, eating disorders are associated with substantial disability. Weight loss and metabolic imbalances can be life threatening with mortality as high as 20 percent over 15 years of followup. Eating disorders may have long-term health consequences, such as osteoporosis. NIMH is committed to funding research to help better understand these devastating disorders. Below are 2003 and 2004 highlights of this research.

Eating Disorders Show High Co-morbidity with Anxiety Disorders

Researchers performed structured interviews and measured aspects of anxiety in order to determine the frequency of anxiety disorders in patients with eating disorders and to understand how anxiety disorders are related to eating disorder illness. These measures were compared to a group of unaffected women in the community. Two thirds of individuals with eating disorders had one or more lifetime anxiety disorders, most commonly obsessive-compulsive disorder (41 percent) and social phobia (20 percent). A majority of the participants reported the onset of OCD, social phobia, specific phobia, and generalized anxiety disorder in childhood, before they developed an eating disorder. People with a history of an eating disorder, who were not currently ill and never had a lifetime anxiety disorder diagnosis, still tended to be anxious, perfectionistic, and harm avoidant. This study demonstrates that the prevalence of anxiety disorders in general, and OCD in particular, was much higher in people with anorexia nervosa and bulimia nervosa than women without these disorders. Anxiety disorders commonly had their onset in childhood before the onset of an eating disorder, supporting the possibility that anxiety is a vulnerability factor for developing anorexia nervosa or bulimia nervosa.

(Kaye, W.H., Bulik, C.M., Thornton, L., Barbarich, N., and Masters, K. Co-morbidity of anxiety disorders with anorexia and bulimia nervosa. *Am J Psychiatry*. 2004 Dec;161(12):2215-21.)

Altered Serotonin Receptor Binding after Recovery from Bulimia-type Anorexia Nervosa

Several lines of evidence suggest that a disturbance of serotonin pathways may contribute to the cause of anorexia nervosa (AN) and bulimia nervosa (BN). This study used positron emission tomography (PET) to investigate the brain serotonin 2A receptor, which could contribute to disturbances of appetite and behavior in AN and BN. Recovered normal weight women with bulimia were compared to healthy control women. Women with a history of bulimia had lower serotonin binding than controls. This study extends research suggesting that altered serotonin activity persists after recovery from bulimia-type AN. Altered serotonin transmission after recovery also supports the possibility that this may be a trait-related disturbance that contributes to the underlying cause of eating disorders.
(Bailer, U.F., Price, J.C., Meltzer, C.C., Mathis, C.A., Frank, G.K., Weissfeld, L., McConaha, C.W., Henry, S.E., Brooks-Achenbach, S., Barbarich, N.C., and Kaye, W.H. Altered 5-HT(2A) receptor binding after recovery from bulimia-type anorexia nervosa: Relationships to harm avoidance and drive for thinness. *Neuropsychopharmacology*. 2004 Jun;29(6):1143-55.)

Lowered Levels of Tryptophan Reduces Anxiety in Patients with Anorexia Nervosa

Recent studies have raised the question as to whether a dysregulation of the neurotransmitter serotonin may contribute to the alterations in mood seen in anorexia nervosa (AN). People with AN tend to be anxious, obsessional, perfectionistic, and harm avoidant. These traits persist after recovery. It has been suggested that increased activity of brain serotonin systems could contribute to this condition. Dieting in AN, which serves to reduce plasma levels of tryptophan, may serve to reduce symptoms of dysphoric mood. Both women with active anorexia nervosa and those recently recovered from the illness had a significant reduction in

anxiety on the day of the acute tryptophan depletion, compared with the placebo day. These data demonstrate that a dietary-induced reduction of tryptophan, the precursor of serotonin, is associated with decreased anxiety in people with AN. Restricting dietary intake may represent a mechanism through which individuals with AN modulate a dysphoric mood.
(Kaye, W.H., Barbarich, N.C., Putnam, K., Gendall, K.A., Fernstrom, J., Fernstrom, M., McConaha, C.W., and Kishore A. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. *Int J Eat Disord*. 2003 Apr;33(3):257-67.)

Significant Linkage on Chromosome 10p in Families with Bulimia Nervosa

Bulimia nervosa (BN) is strongly familial and additive genetic effects appear to contribute substantially to the observed familiality. In turn, behavioral components of BN, such as self-induced vomiting, are reliably measured and heritable. To identify regions of the genome harboring genetic variants conferring susceptibility to BN, researchers conducted a linkage analysis of multiplex families with eating disorders that were identified through a proband with BN. Linkage analysis revealed a susceptibility locus for bulimia on the short arm of chromosome 10. Suggestive linkage was also found on chromosome 14q. Further studies to find the candidate genes in these regions are planned.
(Bulik, C.M., Devlin, B., Bacanu, S.A., Thornton, L., Klump, K.L., Fichter, M.M., Halmi, K.A., Kaplan, A.S., Strober, M., Woodside, D.B., Bergen, A.W., Ganjei, J.K., Crow, S., Mitchell, J., Rotondo, A., Mauri, M., Cassano, G., Keel, P., Berrettini, W.H., and Kaye, W.H. Significant linkage on chromosome 10p in families with bulimia nervosa. *Am J Hum Genet*. 2003 Jan;72(1):200-7.)

Schizophrenia and Other Mental Illnesses

There are clinically important gender differences of schizophrenia and other serious mental disorders. Women with schizophrenia display more affective symptoms and generally have better functioning than men. They are older when they have their first onset of mental illness. The protective role of estrogens against psychosis in schizophrenia has been suggested from both preclinical and clinical data. Issues of childbearing complicate treatment choices; and rehabilitative services may require them to be away from their children. Women with serious mental illnesses may be counseled to maintain psychotropic medications in order to forestall new episodes. However, drugs used to treat or protect against recurrences vary in teratogenic potential. Low risks are associated with typical neuroleptic drugs used to treat psychosis, moderate risks with lithium, and higher risks with older anticonvulsants, such as valproic acid and carbamazepine. Little is known about teratogenic risks with other newer-generation anticonvulsants and atypical antipsychotics. Below are highlights of 2003 and 2004 NIMH research relevant to women with schizophrenia and other mental illnesses.

Decreased Glucocorticoid and Estrogen Receptor Alpha Messenger Ribonucleic Acid Levels in the Amygdala of Patients with Major Mental Illness

The amygdala is a part of the brain involved in the stress response and the regulation of emotional behaviors, both of which are disrupted in patients with neuropsychiatric illnesses. Because glucocorticoids are mediators of the stress response, researchers hypothesized that glucocorticoid receptor (GR) messenger ribonucleic acid (mRNA) levels might be altered in this part of the brain. Because there are also known sex differences in mental illness, they also hypothesized that estrogen receptor alpha (ER alpha) mRNA expression might be altered in the amygdale. Using specimens from a brain bank the authors found that compared with control subjects, GR mRNA expression was reduced in the parts of the amygdala in schizophrenia and bipolar disorder. Estrogen receptor alpha mRNA levels were reduced in the other parts of the amygdala in major depressive disorder and bipolar disorder. These results support a role for both stress and sex hormone receptor alterations in mental illness.
(Perlman, W.R., Webster, M.J., Kleinman, J.E., and Weickert, C.S. Reduced glucocorticoid and estrogen receptor alpha messenger ribonucleic acid levels in the amygdala of patients with major mental illness. *Biol Psychiatry*. 2004 Dec 1;56(11):844-52.)

A Sexually Ddimorphic Ratio of Orbitofrontal to Amygdala Volume is Altered in Schizophrenia

Sexual differences in brain structure have been correlated with differences in behavior in healthy men and women. Although there are known sex differences in schizophrenia that correlate with structural differences in the brain, their relationship to a specific brain volume ratio that has been shown to be different in patients with schizophrenia, compared with unaffected individuals (orbitofrontal to amygdala (OAR) ratio), had not been examined. Investigators used magnetic resonance imaging and found that men with schizophrenia showed a pattern in the brain that was more like normal women, whereas women with schizophrenia showed a more masculine pattern. In men, increased amygdala volume was associated with greater symptom severity, whereas in women higher volumes of both amygdala and orbitofrontal regions were associated with lesser severity of negative symptoms. These opposite OAR abnormalities, whereby men show feminization and women masculinization, suggest gender-mediated effects of the underlying neuropathologic processes. The correlations with symptom severity suggest that neuroanatomic abnormalities in OAR reflect compensatory brain changes. In a related study, these authors revealed a significant sex difference in another region of the brain, the corpus callosum.
(Gur, R.E., Kohler, C., Turetsky, B.I., Siegel, S.J., Kanes, S.J., Bilker, W.B., Brennan, A.R., and Gur, R.C. A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biol Psychiatry*. 2004 Mar 1;55(5):512-7.)
(Dubb, A., Gur, R., Avants, B., and Gee, J. Characterization of sexual dimorphism in the human corpus callosum. *Neuroimage*. 2003 Sep;20(1):512-9.)

Factors Affecting Community Functioning in Women with Serious Mental Illness

Community functioning is an important aspect of assessment and treatment of individuals with serious mental illness. While control of symptoms is an important factor, other conditions can affect the successful functioning of women with severe mental illness. Researchers found that among 332 low-income mothers with serious mental illness current psychiatric symptoms had the greatest effect on community functioning, but that financial concerns and social support were also significant predictors of functioning. Additionally, use of mental health services was a significant moderator of the effect of social stress on community functioning.
(Bybee, D., Mowbray, C.T., Oyserman, D., and Lewandowski, L. Variability in community functioning of mothers with serious mental illness. *J Behav Health Serv Res*. 2003 Jul-Sep;30(3):269-89.)

Prevalence of Obesity in the Severely Mentally Ill: Sex Differences

Individuals with severe and persistent mental illness (SPMI) have weight problems, possibly even greater than the obesity epidemic in the general population. Although atypical antipsychotics cause weight gain, their contribution to obesity has not been characterized in a community setting where individuals may take multiple medications. The authors investigated obesity prevalence in patients with severe and persistent mental illness and a sample of the general population adjusted to SPMI demographic characteristics. The results indicate that both men and especially women with SPMI had a higher prevalence of obesity than the general population. A fourfold association between atypical antipsychotics and prevalent obesity was found in men but not in women; further work should clarify mechanisms of obesity in the SPMI.
(Daumit, G.L., Clark, J.M., Steinwachs, D.M., Graham, C.M., Lehman, A., and Ford, D.E. Prevalence and correlates of obesity in a community sample of individuals with severe and persistent mental illness. *J Nerv Ment Dis*. 2003 Dec;191(12):799-805.)

Absence of Co-morbid Substance Disorder Predicts Remission in Borderline Personality Disorder

During a 6-year prospective follow-up of patients with borderline personality disorder, researchers assessed the prevalence of co-morbid psychiatric disorders. Results revealed that, over time, paients with borderline personality disorder generally experienced declining rates of many psychiatric disorders. Those whose

borderline personality disorder improved over time experienced substantial decline in all co-morbid disorders assessed. Absence of substance use disorders was a far stronger predictor of remission from borderline personality disorder than was the absence of posttraumatic stress disorder, mood disorders, other anxiety disorders, or eating disorders, respectively. The results of this study suggest that co-occurring psychiatric disorders are less common over time in patients with initially severe borderline personality disorder and that substance use disorders are most closely associated with the failure to achieve remission from borderline personality disorder.
(Zanarini, M.C., Frankenburg, F.R., Hennen, J., Reich, D.B., and Silk, K.R. Axis I comorbidity in patients with borderline personality disorder: 6-year follow-up and prediction of time to remission. *Am J Psychiatry*. 2004 Nov;161 (11):2108-14.)

Health Behavior, AIDS, and Mental Health Disparities

A landmark 2001 Surgeon General's report, entitled Culture, Race, and Ethnicity, highlighted disparities in mental health services for racial and ethnic minorities in the United States. Barriers to access include: stigmatization of mental illness among different cultural groups, and limited financial resources. A subcommittee of that commission was formed to consider research needs in relation to ethnic minorities in the United States and to make policy recommendations. The Subcommittee on Cultural Competence of The New Freedom Commission on Mental Health recently issued a report calling for more research on the role of culture and social context in mental health and on the provision of culturally appropriate care as such care relates to better mental health outcomes. Research on health behaviors related to AIDS is also increasingly important, particularly to minorities, where African American women are experiencing a disproportionate increase in HIV infection. Below are highlights of 2003 and 2004 NIMH-funded research addressing AIDS and health disparities in samples of ethnic/minority women.

Sex, Ethnicity, and Antipsychotic Medication Use in Patients with Psychosis

Previous studies suggested that African American patients with psychotic disorders receive higher doses of antipsychotic medication than white patients, are more likely to receive depot antipsychotics, and are less likely to be prescribed second-generation antipsychotics. African American men, in particular, may be most likely to receive excessive doses of antipsychotics and depot antipsychotics, although this is less clear. Few studies have examined how sex and ethnicity interactions affect treatment of psychotic disorders. In this study, the authors examined whether the interaction of sex and ethnicity predicted the use of depot antipsychotics and the dosing of antipsychotics in a sample of inpatients with psychotic disorders. African American men received depot antipsychotic medication more frequently than African American women and white patients. African American men and women with psychotic mood disorders were also more likely to be discharged on high antipsychotic doses, compared with white patients. There were no ethnic or sex differences in the dosing of antipsychotics for the treatment of schizophrenia spectrum disorders or in the use of second-generation antipsychotics.
(Arnold, L.M., Strakowski, S.M., Schwiers, M.L., Amicone, J., Fleck, D.E., Corey, K.B., and Farrow, J.E. Sex, ethnicity, and antipsychotic medication use in patients with psychosis. *Schizophr Res*. 2004 Feb 1;66(2-3):169-75.)

Intervention Reduces HIV Transmission and STDs among HIV-infected Women

HIV transmission preventions strategies that focus on HIV-positive women may be key in controlling the spread of the disease. Given such need, researchers created the WiLLOW (women involved in life learning from other women) intervention, which emphasizes gender pride, communication and safer sex skills, and healthy sexual and social relationships. In a randomized controlled trial of women living with HIV, researchers evaluated the efficacy of WiLLOW in reducing HIV transmission risk behaviors and the occurrence of STDs, as well as enhancing HIV-preventative psychosocial and support factors. Over the 12-month follow-up, women in the WiLLOW intervention had

fewer episodes of unprotected intercourse, lower incidence of bacterial STDs, greater HIV knowledge and condom-using skill, larger social support networks and fewer partner-related barriers to condom use. This is the first trial to demonstrate that prevention strategies to the specific psychosocial needs of HIV-positive women can lead to reductions in risky sexual behavior and incident bacterial sexually transmitted diseases. (Wingood, G.M., DiClemente, R.J., Mikhail, I., Lang, D.L., McCree, D.H., Davis, S.L., Hardin, J.W., Hook, E.W. 3rd, and Saag, M. A randomized controlled trial to reduce HIV transmission risk behaviors and sexually transmitted diseases among women living with HIV: The WiLLOW Program. *Journal of Acquired Immune Deficiency Syndromes*. 2004 Oct 1; 37:S58-S67.)

Preventing HIV in a High-risk Group: African American Girls

Sexually active adolescents have an increased risk of HIV infection; among adolescents, African American girls are at particularly high risk, far more so than their white or Hispanic female peers, and more so than any group of male adolescents. To address this health disparity, NIMH grantees conducted a randomized controlled trial to evaluate a new HIV-preventive intervention for reducing risky behaviors and sexually transmitted diseases (STDs) and enhancing prevention behaviors in this population. In this community-based study, educational sessions were held at family medicine clinics. The intervention included four 4-hour group sessions given on consecutive Saturdays at a family medicine clinic. Each session was conducted by a trained African American female health educator and two African American peer educators. The control group also received four 4-hour sessions, but on different topics. After 1 year, intervention participants were more likely than the control group to exhibit HIV-preventive behaviors, such as having protected sex at last intercourse. They were also less likely to have had a new sex partner in the past 30 days. Promising effects were also observed for prevention of sexually transmitted diseases (STDs) and self-reported pregnancy. The investigators concluded that interventions for African American adolescent girls that are gender-tailored and culturally relevant can enhance HIV-preventive behaviors, skills, and mediators, and may reduce pregnancy and STDs.
(DiClemente, R.J., Wingood, G.M., Harrington, K.F., Lang, D.L., Davies, S.L., et al. Efficacy of an HIV Prevention Intervention for African American Adolescent Girls: A Randomized Controlled Trial. *JAMA*. 2004, 292: 171-9.)

Tailored Outreach Efforts Help Low-income, Young Minority Women Overcome Depression

Impoverished ethnic minority patients are less likely to obtain care for depression than white patients, and are less likely to receive appropriate treatment when they do seek care. Young minority women, a group at high risk for depression, often have histories of trauma, as well as financial and child care burdens, making it personally and logistically difficult to receive care. Results from a randomized clinical trial show that over a 6-month period, low-income minority women benefited from depression treatment (medication or cognitive behavior therapy) when it was paired with intensive outreach and encouragement to support the interventions. Not only did women achieve lower levels of depressive symptoms, but they also gained higher levels of social and personal functioning in daily life. Outreach support was an essential part of the study. In comparison to referral to community care, medications were more effective in reducing depressive symptoms, improving personal functioning, and increasing ability to care and interact with others. Cognitive behavior therapy was better than community care in reducing depressive symptoms and increasing the ability to care and interact with others, but had no effect on personal functioning. Most depression treatment efficacy trials are based on samples of predominantly white patients in academic psychiatric settings, but it has never been clear whether such treatment benefits the underserved. This effort demonstrates that with additional outreach efforts, depressed young ethnic minority women with financial and family care burdens and histories of trauma can clearly benefit from treatment. (Miranda, J., Chung, J.Y., Green, B.L., Krupnick, J., Siddique, J., Revicki, D.A., and Belin, T. Treating depression in predominantly low-income young minority women: A randomized controlled trial. *JAMA*. 2003, 290(1):57-65.)

Mental Disorders among Native American Women in Primary Care Settings

Researchers examined the lifetime and the past-year prevalence of common mental disorders among American Indian and Alaska Native women who presented for primary care. Using standard health questionnaires and diagnostic interviews, researchers examined associations between psychiatric disorders and sociodemographic variables, boarding school attendance, and psychopathology in the family of origin. The findings of this study indicate high rates of alcohol use disorders, anxiety disorders, and anxiety/depression co-morbidity in Native American women compared with non-American Indian/Alaska Native women in primary care settings. Additionally, in a separate study, researchers examined the prevalence of a history of childhood abuse or neglect in American Indian women using primary care services. Approximately three-quarters of the women reported some type of childhood abuse or neglect and over 40 percent reported exposure to severe maltreatment. Severity of child maltreatment was associated in a dose-response manner with lifetime diagnosis of mental disorders. It was strongly associated with lifetime PTSD and was moderately associated with lifetime substance use disorders, mood disorders, and with two or more disorders. Findings from these two studies underscore the need for culturally appropriate mental health care in primary care settings and illustrate the need to screen for psychiatric disorders as well as a history of childhood abuse and neglect in Native women.
(Duran, B., Malcoe, L.H., Sanders, M., Waitzkin, H., Skipper, B., and Yager, J. Prevalence and correlates of mental disorders among Native American women in primary care. *Am J Public Health*. 2004 Jan;94(1):71-7.)
(Duran, B., Malcoe, L.H., Sanders, M., Waitzkin, H., Skipper, B., and Yager, J. Child maltreatment prevalence and mental disorders outcomes among American Indian women in primary care. *Child Abuse Negl*. 2004 Feb;28(2):131-45.)

Urban Women Experiencing Intimate Partner Violence at Greater Risk for HIV

Researchers explored the association between intimate partner violence (IPV) and HIV risk among urban, predominantly minority women. Interviews were conducted with 1,590 women, predominantly African American and Latina, attending hospital-based health care clinics. Approximately one in five women reported experiencing IPV in their current primary heterosexual relationships; one in eight women reported experiencing IPV in the preceding 6 months. Compared to women who reported no IPV in their primary relationships, women reporting past or current IPV perpetrated by their primary partners were more likely to report having multiple sexual partners, a past or current sexually transmitted infection (STI), inconsistent use or nonuse of condoms, and a partner with known HIV risk factors. These findings indicate that urban minority women experiencing IPV are at elevated risk for HIV infection. These findings carry important implications in the efforts to improve HIV and IPV risk assessment protocols and intervention/prevention strategies for women in primary health care settings.
(Wu, E., El-Bassel, N., Witte, S.S., Gilbert, L. and Chang, M. Intimate Partner Violence and HIV Risk Among Urban Minority Women in Primary Care Settings. *AIDS and Behavior*, 2003, 7(3):291-301.)

Initiatives

The Women's Mental Health Program is located organizationally within the Office for Special Populations, Office of the NIMH Director. The women's mental health position was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational focal point for women's mental health science communication, and liaison with the NIH Office of Research on Women's Health and other governmental and non-governmental organizations interested in women's issues. The Office for Special Populations also has program positions dedicated to minority research training, health disparities, and rural mental health. The office coordinates

NIMH activities that serve to fulfill the Congressional mandate for tracking the inclusion of women and minorities in clinical research.

The Women's Mental Health Team serves as the focal point for coordination of NIMH scientific activities related to women's health and sex/gender differences research. Members of the consortium include representatives from all five extramural research divisions as well as researchers from the Intramural Program. Other components represented in consortium membership include the following offices: Communications and Public Liaison, Science Policy and Program Planning, Constituency Relations and Public Liaison, and the Executive Office. Consortium members work across disciplinary boundaries to plan workshops and conferences and to prepare/review science reports and Program Announcements related to women's mental health.

Program Announcements (PAs)

The announcements listed below were active in 2003 and 2004 and had a significant focus on women's mental health research.

- **Women's Mental Health and Sex/Gender Differences Research**
  http://grants1.nih.gov/grants/guide/pa-files/PA-03-143.html
  (PA-03-143)

- **Women's Mental Health in Pregnancy and the Postpartum Period**
  http://grants.nih.gov/grants/guide/pa-files/PA-03-135.html
  (PA-03-135)

- **Mental Health Consequences of Violence and Trauma**
  http://grants.nih.gov/grants/guide/pa-files/PA-04-075.html
  (PA-04-075)

- **Supplements to Promote Re-entry into Biomedical and Behavioral Research Careers**
  http://grants1.nih.gov/grants/guide/pa-files/PA-04-126.html
  (PA-04-126)

Request for Applications (RFAs)

In 2003 and 2004, the NIMH also participated in the following ORWH Requests for Applications.

- **Research on Interventions for Anorexia Nervosa**
  http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-04-002.html
  (RFA-04-002)

- **Exploratory/Developmental Translational Grants for Borderline Personality**
  http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-04-006.html
  (RFA-04-006)

- **Building Interdisciplinary Careers in Women's Health**
  http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-05-002.html
  (RFA-05-002)

Conferences and Meetings

- **Next Steps in Borderline Personality Disorder**
  2003 Family Perspectives Conference: Borderline Personality Disorder and Co-Occurring Disorder; NIMH International Think Tank for More Effective Treatment of Borderline Personality Disorder
  These series of meetings were focused on fostering translational research in borderline personality disorder, as well as to review known treatments and foster the development of new treatments for this disorder. The Family Perspectives conference also focused on the disseminations of research information, as well as seeking input from families, professionals, and consumers who deal with this disorder. Funding for these meetings was provided by the NIMH, as well as through a conference grant, R13 MH 68456.

- **Preventing Suicide and Attempted Suicide in Women Across the Lifecourse**
  This June 2004 conference was organized by the University of Rochester. The meeting goals were to define and disseminate the most effect methods for suicide prevention in women across different life stages.

Funding for the meeting was provided by an NIMH grant, R13 MH 62073.

- **National Rural Women's Health Conference: Improving the Health of Women—Meeting the Challenges of the Rural Setting**
  This September 2004 conference was organized by Penn State. The meeting goals were to improve health-related quality of life for women of all ages who reside in rural communities. Funding for the meeting was provided by an NIMH grant, R13 MH 66413.
- **International Conference on Eating Disorders**
  This June 2004 conference was designed to address high priority areas of research in eating disorders, as well as support junior investigators in this field. Funding for the meeting was provided by an NIMH grant, R13 MH 064468.
- **Dysfunctional Appetitive Behavior: Developing Interdisciplinary Approaches to Understanding Substance Abuse and Eating Disorders**
  This September 2004 meeting was focused on basic mechanisms of appetite disregulation with the goal of better understanding how these mechanisms might serve as underpinnings of both eating and substance abuse disorders.
- **Bench to Bedside: Estrogen as a Case Study**
  This September 2004 meeting was co-sponsored by the NIA, the NIMH, and the ORWH and was focused on bringing basic and clinical researchers interested in menopause and estrogen therapy research together, with the goal of examining the discrepancies between the findings of the Women's Health Initiative on brain and cognitive functions and findings from basic research.
- **National Perinatal Depression Collaborators Meeting**
  The NIMH co-funded this September 2004 meeting that brought together federal agencies, professional organizations, and advocacy groups in order to obtain feedback on a national report on perinatal depression, as well as to facilitate collaborative projects on perinatal depression among participant groups.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease, a burden borne by every age group, by every segment of society, by people all over the world. Most nervous system disorders affect men and women equally, but certain disorders are more prevalent in, or are of special interest to, women. Major examples include multiple sclerosis, pain, stroke, and epilepsy. The NINDS supports basic, translational, and clinical research on these and other neurological disorders.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that causes inflammation, demyelination, and damage to nerve fibers. MS is one of the most common neurological disorders leading to disability in young adults. The disorder is usually characterized by attacks of muscle weakness; coordination, balance, or vision problems; abnormal sensations; and sometimes cognitive impairments. Hormonal factors may influence MS; some forms of MS are twofold more frequent in women and fewer relapses are reported during pregnancy. NINDS-sponsored research is underway to compare the efficacy of standard therapies alone and in combination (CombiRx trial); to develop methods to protect against damage to myelin and nerve fibers; to identify MS biomarkers; and to better understand the genetic, hormonal, and environmental contributions to the disease.

Chronic pain results from pain signals that keep firing in the nervous system for weeks, months, or even years. Some chronic pain conditions, like migraine headaches or fibromyalgia, tend to be diagnosed more often in women than in men. Treatments for chronic pain can include medication, acupuncture or relaxation techniques, local electrical stimulation or brain stimulation, psychotherapy or behavior modification therapies, or surgery. The NINDS research portfolio contains a broad range of projects focused on understanding pain pathways and mechanisms of pain processing, modulation, and regulation, and pain management. Specific topics

include: research about the peripheral, spinal, brainstem, and cortical mechanisms and pathways of pain; about neuropeptide, cholinergic, and glutamate systems involvement in pain; about the mechanisms of anesthesia and analgesia; and about central and post-stroke pain, migraine, neuropathic pain, visceral pain, pelvic pain, painful peripheral neuropathies, including diabetic and HIV-associated neuropathies, back pain, muscle pain, cancer pain, and inflammatory pain.

Strokes are caused by a rapid disruption in the blood supply to part of the brain as a result of blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or a sudden severe headache. Stroke is the third leading cause of death in the United States, and a major cause of disability in both women and men. Although women in general have a lower risk of stroke than men, because of their longer life expectancy they account for 60 percent of stroke fatalities. The NINDS stroke research program ranges from basic investigation of stroke mechanisms through large studies of risk factors and clinical trials aimed at prevention and treatment. Interventions under investigation include drugs, surgery, vitamins, physical therapy, and psychosocial modalities. Research is also targeted to special issues of stroke in various populations, including women. For example, an NINDS-sponsored prospective cohort study is examining the risk of stroke in patients with systemic lupus erythematosus (SLE), an autoimmune disease that predominantly strikes women.

Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. While anti-epileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for some the seizures are resistant to therapy or the treatments cause unacceptable side effects. Women with epilepsy can face special problems, such as increased seizure frequency during phases of the menstrual cycle (called catemenial epilepsy). Female patients taking selected AEDs must consider changing medications if they wish to become pregnant, since certain AEDs can cause higher-than-normal rates of birth defects. In addition to many basic and translational studies of epilepsy and epileptogenesis, the NINDS also supports clinical research in epilepsy. Several of these clinical projects are targeted to issues of special interest to women, such as hormonal influences on seizures and neurodevelopmental effects of *in utero* exposure to AED therapy.

Accomplishments

Women's Health Coordination

The NINDS designates one staff member from the Division of Extramural Research as the Institute's Representative to the NIH ORWH Coordinating Committee on Research on Women's Health. A second staff member, currently from the NINDS Office of Science Policy and Planning, serves as an alternate.

Multiple Sclerosis

Antibody Therapy for Multiple Sclerosis

Standard therapy is not effective in all patients with multiple sclerosis (MS). A phase II trial conducted in a small group of patients suggests that daclizumab (Zenapax®)—an antibody designed to block the expansion of human immune cells—is a safe and well-tolerated add-on therapy, and can reduce new inflammatory lesions by nearly 80 percent after several months of treatment. Researchers also observed improvements in several clinical outcome measures, including a timed walking test. These data provide support for further clinical exploration of daclizumab in individuals with MS. (Bielekova, et al. 2004. *PNAS* 101:8705-8708.)

Activation of Autoimmune Cells by Bacterial Products

Both genetic and environmental factors contribute to autoimmune disease, and researchers have shown in animal models of MS that genetics can also play a role in disease resistance/susceptibility. Investigators funded by the NINDS and the NIAID have demonstrated in mice that antigen-presenting cells—cells that initiate some immune responses—can play a key role in disease resistance, but can be overcome by agents such as bacterial products that can stimulate the immune system on a broad level. This study demonstrates the interplay

between genetics and environmental factors, and explains how microbial agents might be able to trigger autoimmunity. (Waldner, et al. 2004. *J. Clinic. Investigation* 113:990-7.)

Pregnancy Hormones and Immune Modulation

The disproportionate prevalence of MS in women, and the temporary improvements in MS sometimes observed during pregnancy, suggest that hormone modulation might be used as a therapeutic strategy. Recently, NIAID- and NINDS-supported researchers evaluated the effects of estriol—a hormone that increases during pregnancy—on immune markers in women with MS. The results indicated that the immune systems of estriol-treated patients made smaller amounts of detrimental immune molecules and larger amounts of beneficial molecules, and that these changes appeared to mirror the reduction in brain inflammation observed using MRI. These findings lend support for further pursuit of estriol and other hormone-based therapies. (Soldan et al. 2003. J. *Immunol.*, 171:6267-74.)

Anti-cholesterol Drugs in the Treatment of Multiple Sclerosis

Statins are most commonly known for their cholesterol-lowering effects, but scientists have also noted that these drugs can reduce inflammation. Because inflammation may play a role in MS, NINDS-supported researchers evaluated their efficacy in a mouse model of the disease. Results indicated that the drugs reduced the progression of disabling effects of the disease, and in some cases, reduced paralysis that had already developed. Although the results are encouraging, the mouse model is not a perfect predictor of whether treatments will work in the human disease. Careful trials in people are under way and will determine whether statins should be used to treat MS. (Sawsan et al. 2002. *Nature* 420:78-84.)

Pain

Sex-specific Mechanisms of Analgesia

Researchers, funded in part by NINDS, demonstrated that the melanocortin-1 receptor gene (Mc1r) mediates κ-opioid analgesia in female mice only. The researchers extended these findings to humans by demonstrating that women with red hair and fair skin, two traits associated with variants of the human MC1R gene, also have altered analgesia, displaying significantly higher analgesia in response to a κ-opioiod drug. This effect was seen in women only. This study suggests an unexpected role for MC1R, a gene previously not known to play a role in inhibition of pain, and demonstrates a specific difference in pain modulation in the two sexes. (Mogil, et al. 2003. *PNAS* 100:4867-72.)

NINDS-funded scientists have also found that differences in signaling mechanisms are important contributors to the sex differences in the response to opioid drugs. In normal mice, males display higher pain thresholds than females. However, the researchers found that in mice lacking the gene for a subunit of a brain potassium channel, the pain threshold was reduced in males but not females, eliminating the sex difference. Male mice also exhibited a more pronounced response to the analgesic effect of morphine, which disappeared in the mutant mice. The study suggests that signaling pathways are major contributors to the sex differences in the effectiveness of several analgesic agents. (Mitrovic, et al. 2003. *PNAS* 100:271-6.)

Sex Differences in Pain Perception

Much evidence indicates that women experience painful stimuli as more intense than men do. Nevertheless, some data suggest that sustained low-level pain may be more disturbing to men than to women. An NINDS-supported study evaluated whether pain is more disturbing for men than for women by comparing sensory and emotional aspects of pain across genders. The results demonstrated that females rated both pain intensity and unpleasantness higher than did males. However, men reported more pain-related anxiety than women. (Frot, et al. 2004. *Pain* 108:230-6.)

Stroke

Stroke in Women

Risk factors for stroke include high blood pressure, heart disease, diabetes, and cigarette smoking. Some studies have suggested that the presence of certain antibodies in the blood (called aPL antibodies) may also confer a greater risk of ischemic stroke caused by a blocked blood vessel. The NINDS supports investigators who are

conducting a population-based, case control study of stroke risk factors in women (Stroke Prevention in Young Women Study). These investigators found a modest association between the presence of aPL antibodies and stroke in this population of women. Although further work is needed to understand the exact relationship between aPL antibodies and stroke, it appears as though the antibody-associated stroke risk found in earlier studies is also found in young women. (Brey, et al. 2002. *Stroke* 33:2396-401.)

Epilepsy

Seizure Frequency and Menstruation in Women with Epilepsy

For some women with epilepsy, changes in seizure frequency can be associated with the menstrual cycle. This pattern of seizure clustering is called catamenial epilepsy. Interim results from a prospective, multi-center investigation of seizure frequency during the four phases of the menstrual cycle in women with intractable epilepsy found that nearly 40 percent of the female subjects had catamenial epilepsy. Seizures were more frequent either during the time of menstruation or during the ovulatory phase of the menstrual cycle. These early results suggest that one in three women with epilepsy may have catamenial epilepsy. Further studies to investigate hormonal influences on seizure frequency are currently underway. (Herzog, et al. 2004. *Ann Neurol* 56: 431-34.)

Seizure Frequency and Menopause in Women with Epilepsy

Previous studies have shown that seizures can lead to a disturbance in reproductive hormone levels in both women and men. Investigators conducted a retrospective analysis of postmenopausal women with epilepsy to determine whether there was a relationship between the frequency of seizures and age at menopause. Women with epilepsy were divided into three groups according to seizure frequency: low (less than 20 seizures in their lifetime); medium (more than 20 seizures in their lifetime, but less than one seizure per month on average); or high (one or more seizures per month for most of their illness). The results suggest that women with a history of many seizures may undergo menopause at least 3 years earlier than the general population or women who have had fewer seizures. (Harden, et al. 2003. *Neurology* 61:451-55.)

Initiatives

Program Announcements (PAs)

- **Neurovascular Mechanisms of Brain Function and Disease**
  Encourages studies to improve understanding of the dynamic interactions between the brain's blood vessels, glia, neurons, and the extracellular matrix. These interactions are important in stroke, MS, and other neuroinflammatory and degenerative disorders. (PAS-04-072)

- **Neurobiology of Persistent Pain Mediated by the Trigeminal Nerve**
  Invites applications to advance understanding of the neurobiology of persistent pain mediated by the trigeminal nerve and to develop effective therapeutic strategies to alleviate pain associated with disorders of myofascial, nervous, or skeletal tissues of the head and face, which are innervated by this nerve. (PA-03-173)

- **Neuroprotective CNS Barriers in Neurological Diseases**
  Invites studies to improve the understanding of protective barriers in the CNS. In MS, it is particularly important to understand how immune cells cross the blood–brain barrier. This solicitation also encourages studies to enhance the effectiveness of drug and gene delivery strategies for treatment of neurological diseases, including stroke, MS, and other disorders of special interest to women. (PAS-03-165)

- **Biobehavioral Pain Research**
  Encourages applications to study individual differences in pain responses that may be due to factors such as genetic differences, endocrine activity, neural activity, immune function, psychological state, developmental stage, cognitive capacity, disability state, age, gender, social context, and cultural background. (PA-03-152)

- **Neurobiology of Complex Regional Pain Syndrome/Reflex Sympathetic Dystrophy**
  Encourages a broad range of research proposals to investigate the neurobiological

mechanisms and epidemiology of complex regional pain syndrome (CRPS)/reflex sympathetic dystrophy (RSD). (PAS-03-120)

- **Basic and Clinical Research on Rett Syndrome and MECP2**
  Invites developmental, molecular, genetic, pathophysiological, and therapy development projects or clinical studies to understand and treat Rett syndrome. (PA-03-097)

- **Increasing Quality of Life in Mobility Disorders**
  Encourages research applications that focus on improving the quality of life for people living with mobility limiting disorders, such as MS or stroke, by managing the physical symptoms and psychosocial consequences that occur as a result of the primary or secondary condition. (PA-02-111)

Request for Applications (RFAs)

- **Hyperaccelerated Award: Mechanisms in Immunomodulation Trials**
  Requests research applications for add-on mechanistic studies associated with clinical trials of immunomodulatory interventions for immune system-mediated diseases, such as MS. (RFA-AI-04-001)

Conferences and Workshops

- **Biomarkers in Multiple Sclerosis**
  In April 2004, the NINDS held a workshop on biomarkers in MS to evaluate current knowledge and usefulness of biomarkers for the diagnosis of MS, the monitoring of specific disease processes in MS, disease course prediction, and assessment of therapies. Participants included a wide range of national and international experts from fields such as immunology, neuroimaging, cell biology, and clinical care and research. As a next step in developing reliable MS biomarkers, the NINDS intramural scientists, in conjunction with the CombiRx trial, are conducting a large biomarker screening study in approximately 1,000 individuals with MS.

- **Genetics and Multiple Sclerosis: Future Prospects Workshop**
  In September 2003, the NINDS and the National Multiple Sclerosis Society jointly sponsored a workshop on genetics and MS. The goal of this international workshop was the creation of a collaborative MS genetics network that will share strategies, reagents, methods, data, and samples, and will accelerate the discovery of MS susceptibility genes. Genetics researchers from the United States and the United Kingdom have since come together to form the Multiple Sclerosis International Genetics Consortium (MSIGC) which will undertake a NINDS-funded haplotype-based whole genome screen in MS patients.

- **Health Disparities in Epilepsy Planning Panel**
  In November 2002, the NINDS convened a planning panel to address health disparities in epilepsy. The purpose of the planning panel was to discuss issues regarding disparities in epilepsy, and to develop an agenda for research, research capacity building, and outreach. Women, Native Americans, and inner-city populations were included as special groups affected by health disparities in epilepsy.

- **NINDS Stroke Disparities Advisory Panel Meeting**
  In November 2002, the NINDS held a workshop on future research directions in stroke disparities. During this meeting, a nine-member panel of experts was formed to discuss and consider recommendations for advancing research on stroke disparities, including a focus on sex differences in stroke.

Health Disparities among Special Populations of Women

See *Conferences and Workshops* section above for NINDS activities related to health disparities in women.

Plans for Gender Analysis

Gender-specific analysis of clinical trial results can help to detect differences in male and female risk factors and responses to therapy.

Since 1993, the *NIH Grants Policy Guidelines* have required that Phase III trials include sufficient numbers of women to carry out valid analyses of gender differences.

An example in the area of stroke treatment is an NINDS-supported trial that is comparing the efficacy of two procedures (carotid endarterectomy vs. stenting) that unblock a clogged carotid artery in the neck, a condition that presents significant risk factor for stroke. One facet of the trial will examine gender differences in these procedures. Previous research has shown that women may not benefit from carotid endarterectomy as much as men do.

National Institute of Nursing Research

The National Institute of Nursing Research (NINR) supports clinical and basic research to establish a scientific basis for the care of individuals across the life span. Research focuses on the management of patients during illness and recovery, the promotion of healthy lifestyles to reduce the risks for disease and disability, the enhancement of quality of life in those who suffer from chronic illness, and improving care for individuals at the end of life. The NINR's research extends to problems encountered by patients, families, and care givers within a community context, and addresses the special needs of at-risk and underserved populations, with an emphasis on health disparities. The research mission of the NINR is available at *http://www.nih.gov/ninr/research/diversity/mission.html*.

Historically, the focus of women's health research has often centered on reproductive function. However, a growing awareness that women differ from men in their economic, social, political, and environmental circumstances has led to an increase in research devoted to unique issues relating to the health and well being of women across the life span.

In the United States, women generally have lower incomes, more fragmented career tracks, and greater household and caretaker responsibilities than men, and they may be dependent upon a spouse both for income and for health insurance. Women have a longer life expectancy than men, but living longer may mean they develop more chronic conditions and have greater health maintenance and care needs. In their later years, they may lack adequate resources to pay for medications and health care services. Emerging models of health care services need to address these circumstances of women's lives.

Nursing has a long tradition of concern for the health of women and of developing and providing services oriented to the needs of women. Investigators and nurse scientists supported by the NINR have contributed new knowledge addressing women's health, including findings in cardiovascular health, midlife and menopause, aging, cultural and ethnic variations, HIV/AIDS, cancer, chronic disease, women as care givers, and other related issues.

The NINR also continues a strong program of research into women's reproductive health. The events surrounding pregnancy and childbirth have a profound impact on a woman's well being and life experience. Pregnancy influences how a woman sees herself and how others see her. While pregnancy can bring much joy, even a normal pregnancy carries many serious risks. A high-risk pregnancy can affect the mother's future life and outlook, and threaten the health of both the mother and the unborn child. Childbearing also adds roles and responsibilities to which the new mother must adapt, changing a woman's relationship with her partner and her extended family, her status within the community, and her career potential. A pregnancy that ends in miscarriage or a death in infancy can have long-term consequences on a woman's self esteem and ability to cope.

In the United States, pregnancy and childbirth typically bring a woman into frequent contact with health care services. At each encounter, nurses and other providers have the opportunity to enhance the quality of the experience and influence the outcomes. NINR-funded researchers have explored many aspects of care during pregnancy and childbirth through studies that focus on care during pregnancy and delivery, maternal issues in infant care and child development, and adolescent sexuality and pregnancy.

The diverse studies in women's health presented in this report help to give nurses and other healthcare workers greater understanding of the wide range of women's health issues. In addition, they illustrate the NINR's long-standing commitment to research on health disparities and minority health as it applies

to women's health. A large number of studies are devoted to addressing the needs of racial/ethnic minority women, highlighting the importance of examining psychosocial and cultural variables that influence health-seeking behaviors and health outcomes of these populations. Findings from these studies will add to the growing body of literature related to reducing the excess burden of illness borne by racial and ethnic minority women.

Accomplishments

Cardiovascular Health in Women

A number of NINR-funded studies are examining the cardiovascular health of women. Coronary artery disease (CAD) leads to over 250,000 deaths a year among women. Estrogen seems to have a protective effect in cardiovascular health, and after menopause the rate of death from CAD for women approaches that of men. Genetic factors and tobacco use also can increase CAD risk. The diagnosis of CAD often occurs at an older age in women than in men, and symptoms of angina may receive inadequate attention and treatment. To decrease the number of CAD-related deaths in women, there needs to be a greater emphasis on heart-healthy habits and preventive measures.

In a major NINR-funded project, a series of pilot studies on early cardiac symptoms in women led to the development of the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS). Using this tool, female heart attack patients reported a variety of symptoms in the preceding month, including unusual fatigue, sleep disturbance, shortness of breath, indigestion, and anxiety, while fewer than 30 percent had any kind of chest discomfort. Acute symptoms at the time of the heart attack included shortness of breath, weakness, fatigue, cold sweat, and dizziness, with only 57 percent reporting some degree of pressure or pain of the chest. Failure to recognize these early and acute symptoms of an impending MI for women could delay recognition, assessment, and treatment.

In a separate study involving thirty women patients who had experienced a heart attack, all reported improvements in health and in physical, psychosocial, and family functioning at the end of 1 year. Social support and mood state were the best predictors of quality of life. These women placed great importance on family, social support, and mood state during their recovery.

In a study to measure exercise compliance, a group of older women cardiac patients wore a watch-type heart rate monitor during exercise after completing a cardiac rehabilitation (CR) program. Almost 25 percent did not exercise at all, and only 48 percent were still exercising at 3 months. Fewer co-morbidities, more social support, and belief in the benefits of exercise contributed to better exercise amount, frequency, and intensity.

A high proportion of fat in the abdominal region can indicate an elevated risk for both cardiovascular disease and diabetes. Measurement of the abdominal visceral adipose tissue (VAT) in a group of older women found that those with low VAT had the highest levels of the beneficial high density lipoprotein cholesterol (HDL-C), and lowest levels of harmful low density lipoprotein cholesterol (LDL-C) and triglycerides. They also had lower fasting glucose and insulin levels, indicating a decreased risk of diabetes. Women with elevated VAT had poorer cholesterol profiles, as well as impaired glucose tolerance.

Issues of Midlife and Menopause

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

In another study, focus group discussions with midlife women found that they identified major life milestones relating to child bearing and rearing, mortality, changing family relationships, increasing self efficacy, and life experiences, while few singled out menopause. Many of these women felt that their turn had

come to pursue their own interests. Black women tended to note menopause as a normal phase of life, while white women focused more on the signs of aging. Those past menopause often expressed relief at the freedom it brought.

Urinary incontinence (UI) is a common problem for older women in the United States. Using survey data from the Study of Women's Health Across the Nation (SWAN), researchers found that over half of perimenopausal women had experienced UI, with one-quarter reporting moderate to severe leakage. White women experienced the highest incidence, and Hispanic women the lowest. Associated risk factors included number of pregnancies, perimenopausal status, diabetes, obesity, and current smoking.

Women and Aging

Loss of bone mineral density accelerates in women after menopause, increasing the risk of osteoporosis-related fracture. One study followed a group of older women over 2 years to measure changes in bone density. On average, Black women had both a higher body mass index and a higher bone density than white women. For all women, though, bone density decreased with age, especially after menopause.

Several interventions have addressed increasing exercise for older women. One study found that a group of older women living in a retirement community, who received regular supervised exercise sessions over an 8-month period, experienced significant improvements not only in bone density, but also in strength, body sway, and weight. A second study tested two programs to increase exercise among sedentary older women. One involved a series of three motivational sessions to teach the benefits of exercise and relate exercise to common activities. The other involved weekly prompts by telephone and mail to support self-directed exercise behaviors. After the interventions, more women reported engaging in exercise, with women in the prompting group increasing their average time of exercise by over half an hour per week. In a third study, telephone counseling for a group of sedentary older women provided education on the benefits of exercise and helped them set goals to maintain a walking program. Women in this intervention reported more activity than women in non-intervention control groups. In addition, they reported improved vigor and exercise self-efficacy, and a reduction in fatigue. The intervention worked equally well for Black and white women and across income levels.

A diet low in total fat, saturated fat, and cholesterol can reduce cardiovascular disease risk, but in older women this diet can also lower the levels of protective HDL-C. A review of data on a low-fat diet intervention with obese, white, postmenopausal women found that these women did achieve a decrease in harmful LDL-C and total cholesterol. However, women with the apolipoprotein E (APOE)-4 genotype had only a slight drop in HDL-C, and no change in triglycerides, whereas women without this genotype showed a significant decrease in their HDL-C, and raised their triglycerides. A low-fat diet may benefit older women with the APOE-4 genotype, but it may worsen certain risks for other women.

Cultural and Ethnic Health Issues among Women

Regular exercise is an important goal of the Healthy People 2010 initiative, but over one-quarter of women in the United States report minimal leisure-time physical activity, and among women activity levels are lower for Blacks than for whites. Mid-life women enrolled in an individualized, home-based walking exercise program kept an exercise log and met regularly with a research nurse for reinforcement and support. White women participants completed more exercise sessions than Black women, indicating Black women may need more targeted programs to help boost exercise levels.

Violence, specifically physical abuse, is another important health issue for Black women in the United States. Interviews of Black women who had survived a relationship with an abusive male partner found six major themes in the healing process: sharing information with others to break the silence; reclaiming the self and separating from the abuser; renewing the spirit and nurturing the inner self; self-healing through forgiveness; finding inspiration in the future; and engaging in personal or social activism to improve their community. These women found ways not simply to survive an abusive relationship, but to

transform their lives through healing to pursue their own goals.

Asian cultures are often characterized by a strong family commitment to caregiving. From interviews of Asian immigrant women who cared for their aging parents, many reported that caregiving created many overwhelming demands, as most of the women also worked full-time while raising families of their own. They often felt the paradox of trying to uphold the cultural standards of their home country for their parents, while helping their families fit into American life. Many felt blessed to have their parents with them, and learned to utilize their personal and family resources.

Menopause, a vital life-cycle phase for women, is imbued with many personal, social, and cultural meanings. In focus group interviews, older Latina women discussed the role of menopause as a normal adult phase that women must pass through. This is often a time for women to reorient their lives to focus more on personal needs and to reorder the harmony and balance in their life. However, many of the women lacked basic knowledge about the course of menopause and possible ways to manage symptoms.

Health Issues Related to HIV/AIDS

For women living with HIV infection, associated symptoms of fatigue and pain from the disease itself, from the side effects of medications, or from associated infections, can be distressing and frustrating. Several studies have examined symptom management and quality of life for HIV-positive women. One survey showed that over half of HIV-positive women reported difficulty in sleeping, weakness, numbness, poor appetite, nausea, and shortness of breath, and many of the women also scored at high risk for developing depression. In another study, interviews of a small group of HIV-positive women revealed that most felt their sleep quality had decreased since their diagnosis. Poor sleep was often attributed to stress and daily concerns. Coping strategies included quiet activities such as reading, or physical activity such as taking a walk. Some women found that art therapy, massage, Chinese herbs, or certain rituals helped relieve stress.

Sexuality can become an important concern with HIV infection. Interviews with HIV-positive adult women showed that 90 percent remained sexually active. Most of these women were relatively young and reported few physical problems from their infection. While about half always used condoms with sex, over one-third used no safe sex practices. Of the 10 percent of women who were not sexually active, reasons included having no current partner, having no interest, physical problems, and fear of disclosure.

Effective therapy for HIV often requires personal knowledge of the disease and adherence to complex dosing regimens. In another study, most HIV-positive women reported a recent visit to their HIV clinic, but roughly one-third did not know their most recent CD4 cell count or viral load result. Over three-quarters were on a highly active antiretroviral therapy (HAART) regimen, and most HAART-adherent women understood that their medications were supposed to reduce viral load.

Urban, African American, single mothers make up an increasing proportion of newly reported AIDS cases. A survey of mother–child dyads, mostly African American and on public assistance, found that children of HIV-positive mothers displayed elevated signs of externalizing behaviors, such as aggression, and internalizing behaviors, such as depression. Significant contributing factors included maternal HIV-associated stressors, maternal emotional distress, child social support, and child and maternal coping. These results suggest that children of HIV-positive mothers should be routinely assessed for behavioral and adjustment problems.

The emotional responses to the diagnosis may prevent HIV-positive mothers from facing the problem, seeking medical care, or treating their symptoms. A group of low-income, Black HIV-positive mothers received home health visits from a nurse to provide education about HIV, preventing HIV-associated infections, treating gynecologic or genitourinary problems, decreasing depression, and improving health through proper nutrition, exercise, rest, and skin care. The nurse emphasized the relationship between the mother's health and maintaining the maternal role of childcare, and telephone calls in between home visits served to address problems. The mothers reported improved physical function and a reduction in both depressive symptoms and new infections.

A review of over 50 studies involving HIV-positive mothers found that they often struggled with the decision to disclose their HIV status to their children, believed children were the main reason to live and fight the disease, and used motherhood as a source of hope and self-esteem. However, they worried about the transmission of HIV to their offspring, and the negative impact of both the illness and the stigma on their children. Their motherhood experience focused on providing oversight of childcare arrangements, while working to create memories and mementos that would leave them always in the minds and hearts of their children. For these HIV-positive women, motherhood provided a sense of identity and a reason to improve their lives and fight their disease.

Health Issues Related to Breast Cancer

Although early diagnosis of breast cancer can lower disease mortality, compliance with recommended screening protocols is poor. A survey of older women found most had undergone at least one mammogram, but over half of these had not had one within the past year. Those who had never had a mammogram perceived higher barriers to screening than those who had at least one, while those with a current mammogram perceived the greatest potential benefits. In a related study, five mammogram compliance strategies were tested with older women who belonged to an HMO: telephone counseling, in-person counseling, a reminder letter, telephone counseling plus a reminder letter, and in-person counseling plus a reminder letter. All five strategies improved compliance over the non-intervention control group, while the in-person counseling alone plus a reminder letter achieved the highest increase and the greatest cost effectiveness.

After surgery for breast cancer, many women develop lymphedema, a chronic swelling of the arm of the affected side due to impaired lymph drainage. For breast cancer survivors who completed the Lymphedema and Breast Cancer Questionnaire (LBCQ), symptoms of heaviness and numbness in the past year, along with current swelling, were the best predictors of lymphedema. When breast cancer patients of unknown lymphedema status completed the LBCQ, only heaviness and swelling predicted the presence of lymphedema. In another study, older breast cancer patients who received support from a nurse case manager (NCM) stated that the NCM helped them deal with related health care problems; provided education on the disease and its treatment; assisted with daily activities, such as making doctor appointments and completing insurance forms; helped provide transportation; listened to their fears and concerns; and reassured and educated family members.

Health Issues Related to Chronic Illness

Irritable bowel syndrome (IBS), a functional disorder of the bowel with an unknown cause, is more common among women than men, and affects over 10 percent of women in industrial nations. For some women, IBS symptoms may relate to oral contraceptive use or menstrual cycle phase. A survey of women with IBS revealed different primary symptoms consisting of constipation, diarrhea, or an alternating pattern. When the women completed a 5-day symptom diary around the time of their menses, those on oral contraceptives reported lower severity of cognitive, anxiety, and depressive symptoms. Menstrual disturbances, sleep disruption, and cognitive symptoms were strongest in the IBS sufferers with an alternating constipation/diarrhea bowel pattern. In a related study, young women with IBS completed retrospective and daily diary measures of symptoms. Three-quarters of the women reported a history of bloating, most strongly associated with constipation, abdominal pain, and intestinal gas. Bloating was strongly associated with uterine cramping and breast tenderness, but only during the perimenses days. Bloating is a very common symptom in women with IBS, but it may also be associated with menstrual symptoms.

Fibromyalgia (FM), a condition of generalized muscle and joint pain, affects roughly 7 percent of older women, and many sufferers also report poor sleep quality. Women with FM kept a diary of their sleep times and their level of daytime fatigue, and wore an actigraph at night to measure their night-time movement. Compared to a healthy control group, women with FM reported poorer sleep quality and greater fatigue, while actigraph indicators

of total sleep time and sleep fragmentation correlated with self-reported sleep quality and fatigue.

Rheumatoid arthritis (RA) sufferers are encouraged to exercise regularly to maintain joint function. A survey of older women with RA found that they reported being active for an average of 23 hours per week, with housework and gardening comprising most of their physical activity. Over the prior month, 60 percent reported having engaged in vigorous stair climbing, walking, or cycling, and 88 percent had done some moderate-intensity leisure walking. Most active were those women who were still employed or who were involved in housekeeping, but as age increased, physical activity decreased.

Patients with multiple sclerosis (MS), an incurable degenerative disease of the central nervous system that strikes mostly women, experience a variety of symptoms and functional problems that conventional treatments and medications do not ameliorate. A survey of patients with MS showed that almost half had tried a complementary or alternative therapy (CAT), and one-third were using one currently. The CATs reported as most helpful were massage, nutritional supplements, yoga, herbal treatment, and special diets, while those most often reported to have no effect or to be harmful included acupuncture, bee venom, and homeopathy.

Women to Women (WTW), a computer-based health care intervention, provided self-care and treatment information for rural-dwelling women living with a variety of chronic conditions, along with a chatroom to share experiences. Women participating in the WTW program reported that physical responses, such as sleep disturbances, fatigue, and pain, often limited activities and family interactions, while emotional responses of depression, loneliness, frustration, and guilt were stressful and draining. Adaptive responses included humor, hope, and courage. Some women stated that sharing their feelings in the WTW chatroom helped them feel more positive about themselves.

Women as Care Givers

Family care givers, who frequently are older and female, often neglect their own health care. A survey of family care givers over 50 years of age found that most were caring for an ill spouse or parent for an average of 11 hours per day. Roughly one-third rated their own health as fair to poor, and one-quarter required home heath assistance for their own health problems. Few were able to work or travel much outside the home, or were current with routine screening tests or vaccines. However, most reported that caregiving made them feel needed. Female care givers reported more distress from the burdens of care than male caregivers. In another study, comparison of 45 female and 16 male care givers of spouses with Alzheimers found no gender difference in the total number of distressing caregiving experiences. However, men reported a lower subjective sense of burden and perceived stress, had lower levels of depression, anxiety, anger, and somatic symptoms, and reported higher physiologic measures of relaxation.

Miscellaneous Health Issues

Some studies in animal models have shown that the female hormone estrogen has a protective effect on the brain following injury or hemorrhage. However, for patients suffering a traumatic brain injury (TBI), which affects over 5 million Americans each year, an examination of their health outcomes post-injury found that females age 30 years or older had significantly poorer recovery and functional ability after 6 months than either males or younger females.

For patients with an infectious disease, poor medication adherence may fail to cure the disease, increasing the risks and costs for further treatment. A group of women diagnosed with pelvic inflammatory disease were monitored for their compliance with a twice-daily schedule of oral doxycillin. While the women took 70 percent of their total medication dosages, less than half of the doses were taken on the proper 12-hour schedule. Compliance was best among women who had private insurance, worked part-time, did not drink hard liquor, and experienced no medication side effects.

College women are at risk for developing clinical depression, which can hinder their social functioning and academic performance. Interviews with women attending a large

university found that most reported their mothers were more caring than their fathers, while both parents tended to be equally protective. A high level of caring from either parent helped reduce depressive symptoms and negative thinking and increase self esteem. However, parental over-protectiveness had the opposite effect, increasing depression scores and negativity while lowering self esteem.

Care during Pregnancy and Delivery

Each year, doctors advise bed rest for over 700,000 pregnant women deemed at risk for preterm delivery, but bed rest may alter cardiovascular function and metabolism, cause muscle atrophy, and lead to bone mineral loss. A study of a group of women with singleton pregnancies who were hospitalized on bed rest found they had poor maternal weight gain compared to recommended levels. Almost 70 percent of the women delivered prematurely. Although most of the infant birth weights fell within the appropriate range for gestational age, they were significantly below the mean, and low maternal weight gain was linked to low infant birth weights, calling into question the safety and efficacy of routinely prescribing bed rest for many women at risk for preterm delivery.

For pregnant women, high serum levels of homocysteine, an intermediary form of the amino acid cysteine, are associated with the risk of preeclampsia. In a study following a group of pregnant women, roughly half of whom were Black, over one-third were diagnosed with preeclampsia. Compared to the women with normal pregnancies, the preeclamptic women had higher levels of homocysteine, and Black women with preeclampsia had the highest levels of all. Racial differences in homocysteine levels and other risk factors may contribute to the higher incidence of preeclampsia in Black women.

For many women, pregnancy and childbirth can stretch the muscles of the pelvic floor, specifically the levator ani, contributing to the onset of urinary incontinence (UI). Researchers followed a group of primiparous women to evaluate two measures of pregnancy-related UI—the Leakage Index (LI), a simple questionnaire, and the Levator Ani Function Index (LAFI), a clinical measure of pelvic muscle strength. From the LI, women reported the most urine leakage at 35-weeks gestation, and leakage decreased by 6-weeks postpartum. Meanwhile the LAFI score was lowest at 2-weeks postpartum, and highest at 12-months postpartum. Both indices could be useful in assessing UI.

While Mexican American women of childbearing age face many of the stressors common to women of other minority populations, they also have many strengths that can serve as protective factors. A survey of women of Mexican descent who were pregnant or who had recently delivered found that over one quarter were at high risk for depression. Those exposed to the United States from an early age had a higher level of depressive symptoms than those who had spent their childhood in Mexico. For all of the women, a sense of mastery and life satisfaction, and a higher number of adults in the household, contributed to lower depression scores. For the postpartum women, resilience and spiritual beliefs helped combat depression, while low income and inadequate resources to meet needs increased their risk.

An estimated one-sixth of all pregnancies end in miscarriage, and couples experiencing the loss of a pregnancy may have differing emotional responses that affect both the interpersonal and sexual aspects of their relationship. At 1 year after a miscarriage, roughly half of the women respondents in a survey reported a more distant relationship with their partner. Those who reported no change in their interpersonal or sexual relationship had less passive coping strategies and reported less impact from the miscarriage. Only 7 percent of the women reported a closer sexual relationship.

The death of a baby during pregnancy or in the newborn period can be devastating to parents, who may then seek the support of family and friends to help them through this time of loss. Interviews of 22 mothers and nine fathers within the first year after a perinatal loss found that most said that they received emotional support just from the presence of family members and friends, appreciated the sacrifices that others made for them, and found that socialization assisted in the healing process. Many mothers benefited from talking to someone else who had been through a similar experience. However, some parents reported

disappointment when family members did not take time to see them, or made unfeeling or inappropriate comments.

Abuse from an intimate partner is a concern for many pregnancy women. However, the effects of abuse on maternal complications and birth outcomes may be difficult to distinguish from the effects of low income or education and the lack of resources that often accompany an abusive relationship. A review of the records of over 2,000 pregnant women found that roughly 7 percent had suffered recent abuse. Birth outcomes did not differ significantly between abused and non-abused women. However, abused women were more likely to be unmarried and on public insurance, to smoke or use alcohol or drugs, and to have poor maternal weight gain.

Maternal Issues: Infant Care and Child Development

For mothers of preterm infants, separation from the infant during hospitalization and concerns about the infant's survival and the long-term health outlook can contribute to maternal depression and may lead to severe distress. An assessment of a group of mothers of hospitalized preterm infants revealed almost half were at risk for clinical depression. The stress that the mothers perceived in the hospital environment increased the depression scores, whereas the severity of the infant's illness did not. At a 6-month followup, only one-fifth of the mothers remained at risk for depression and the average depression scores for most had dropped significantly. In a separate study, interviews with a small group of neonatal intensive care unit (NICU) mothers found that all reported distress that resembled post-traumatic stress disorder (PTSD), a psychological condition often experienced by trauma victims and characterized by three symptoms: re-experiencing the trauma, avoidance of reminders, and increased arousal or anxiety. For these mothers, re-experiencing took the form of intrusive thoughts and memories related to the NICU and elicited by certain events; avoidance was shown by trying to block out memories of the hospital experience, and heightened arousal often led to maternal hypervigilance and over-protectiveness.

The infant mortality rate for Blacks is roughly twice that for whites, while for Latinos the infant mortality rate is similar to whites. Nurses teamed with health advocates from the community to provide prenatal care and post-natal monitoring to almost 600 low-income, minority mothers, 69 percent of whom were Black, and 31 percent Mexican American. The nurses conducted infant health and development screening, while the health advocates made monthly home visits or telephone calls. After 1 year, Black mothers showed more appropriate parenting expectations and their infants had higher mental development scores than a control group, while Mexican American mothers showed improvement in daily living skills and in playing with their infants.

The incidence of type 1 diabetes among children under 5 years of age has been increasing at roughly 6 percent per year. For parents, dealing with a young child with this chronic disease presents many challenges of managing meals, monitoring glucose levels, and recognizing adverse symptoms. Results from a survey of mothers of young diabetic children found that over half had stopped working due to the increased demands of providing care, which several described as "constant." Primary concerns included hypoglycemic reaction and worry about the child's future. Many reported difficulty in finding a babysitter or daycare provider.

Regular exercise is important to maintaining health, especially in the post-natal period. Interviews of low-income new mothers found that they averaged 17 hours of sleeping or sitting each day, and only 16 minutes engaged in moderate- to high-intensity activity. After the interview, the mothers were asked to wear a pedometer for 3 days as a gauge of their actual activity. The total step counts were only about half of the average expected for normal fit adults, indicating that these mothers need to set realistic goals, find activities they enjoy, and identify barriers to achieving sufficient exercise.

Adolescent Sexuality and Pregnancy

Inner city adolescent mothers, especially from minority populations, face a particularly high risk for HIV exposure due to low socioeconomic status, early onset of sexual activity, history of multiple sex partners, inconsistent

condom use, and experiences of physical or sexual abuse. A survey of minority adolescent mothers found that the average age at first sexual intercourse was 14 years. Over half of the respondents reported having been with more than one partner, and few had used a condom with their last sexual episode. In another study, a group of adolescent mothers, almost two-thirds of whom were Latina, received an early intervention program (EIP) consisting of multiple home visits from a public health nurse designed to enhance maternal caretaking skills and socialization. Compared to mothers who received standard care, more mothers in the EIP were continuing their education, and fewer increased their drug use or had repeat pregnancies, while their infants required fewer total days of hospitalization.

Pregnancy may also bring a sense of maternal identity and protectiveness that can motivate healthy lifestyle changes. An HIV prevention program for minority adolescent mothers, Project CHARM, consisted of class sessions using videos, role playing, and skill-building exercises that addressed HIV knowledge and safe sex practices. After the program, the participants stated improved understanding that their maternal responsibilities included eating healthy foods, decreasing use of cigarettes and drugs, avoiding violent situations, and maintaining a safe home environment for their babies. However, many also had concerns of power and trust with their partners. At a 6-month followup, the adolescent mothers who participated in Project CHARM showed significant gains in AIDS knowledge and in their intention to use condoms, and they reported fewer sexual partners.

Adolescents account for nearly one-quarter of newly diagnosed sexually transmitted diseases (STDs), and adolescent girls are at particular risk because they often partner with older males, may have multiple partners, and are less likely to insist that their partners use condoms. Interviews of sexually active adolescent African American and Latina girls revealed that roughly half had used a condom in their last sexual encounter, almost one-third had been diagnosed with a STD, and one-fifth had been pregnant. Between 70 to 80 percent reported having discussed sex, birth control, STDs and AIDS, and/or condom use with their mothers, and these discussions were related to a lower total number of sexual encounters and unprotected sexual episodes, and an increased self-efficacy in condom use.

Initiatives

Program Announcements (PAs)

- **Health Disparities among Minority and Underserved Women**
  The purpose of this initiative is to stimulate research aimed at reducing health disparities, reducing health risks, and enhancing health promotion among racial/ethnic minority and underserved adult women. Investigators may also focus on the childhood antecedents of adult health disparities. (PA-04-153)

- **Enrolling Women and Minorities in HIV/AIDS Research Trials**
  The NINR is a co-sponsor of this PA. It is the policy of the National Institutes of Health (NIH) that woman and minorities be included in NIH-supported clinical research. These populations are frequently underrepresented in clinical trials, and there is a need to identify and correct barriers to participation by these groups. The goal of this initiative is to support projects that will identify factors negatively impacting the recruitment of women and minorities, and plan and develop mechanisms and interventions that will facilitate the recruitment and retention of these populations in research trials. (PAS-03-168)

- **Reducing Preterm and Low Birth Weight in Minority Families**
  The NINR is a co-sponsor of this PA to encourage collaborative, multidisciplinary biobehavioral research into the mechanisms underlying disparities in pregnancy outcomes, as well as interventions to reduce such disparities. The disparity in pregnancy outcomes among minorities is largely due to preterm delivery (PTD) and low birth weight (LBW), which disproportionately affect these populations. While these problems occur across populations, their greater incidence among minorities makes research with these groups particularly important. This solicitation strongly encourages multidisciplinary biobehavioral

approaches, defined as studies proposed by teams of scientists with the requisite expertise from diverse disciplines (e.g., nursing, medicine, social, behavioral, biological, health sciences, epidemiology) that reflect an integrated framework of social and biologic phenomena. (PA-04-027)

- **Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases**
  The NINR has joined this PA to investigate the pathogenesis and new treatments for primary and secondary lymphedema. Such knowledge will help to improve early diagnosis of affected individuals, the choice and timing of treatment, and genetic counseling. Research is also needed on the pathophysiology of the disorders of skin and subcutaneous tissue secondary to chronic lymphedema, and lymphedema which results from cancers and cancer treatment, with an ultimate goal to develop more targeted and effective therapies. (PA-04-071)

- **Improving Care for Dying Children and Their Families**
  The NINR is co-sponsoring this PA to encourage research that will improve the quality of life for children who are approaching the end of life, the quality of the dying process, and bereavement following the death for the children's families, friends, and other care providers. For this PA, family is defined broadly in terms of traditional families and non-traditional families, including children being cared for in foster situations, by distant relatives, or friends. This research has implications for women, who are most frequently the caregivers of ill and dying children. (PA-04-057)

Workshop

- **Workgroup on Optimizing Pregnancy Outcomes in Minority Populations**
  This workgroup brought together experts in many disciplines, including nursing, medicine, public health, and social work, to explore aspects of health during pregnancy for minority populations. The objectives were to examine the state of the science in pregnancy outcomes in minority populations and foster multidisciplinary research to identify and expand our understanding of psychosocial and environmental factors that affect pregnancy outcomes, with the goal of identifying current gaps in knowledge and soliciting novel study designs and strategies for future research. Papers from this workshop are to be published in upcoming issue of *American Journal of Obstetrics and Gynecology*.

Health Disparities among Special Populations of Women

The NINR continues to develop and implement initiatives related to its "strategic plan on reducing health disparities." The overall focus of this plan is to provide leadership in emphasizing the inclusion of cultural and ethnic considerations throughout the areas of scientific inquiry within the NINR's domain. The three components of the NINR strategic plan on health disparities include research, infrastructure development, and outreach. "Identifying Effective Strategies to Reduce Health Disparities" is one of five NINR research themes for the Future identified in 2003. The research themes document is available at *http://ninr.nih.gov/ninr/research/themes.doc*.

NATIONAL INSTITUTE ON AGING

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2003 and 2004, NIA-supported researchers made important progress in a number of women's health-related areas.

The NIA has several ongoing research initiatives dealing specifically with women's health. These include:

- **Study of Women's Health Across the Nation (SWAN)**
  The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in women of various racial/ethnic backgrounds.

- **The Women's Health Initiative Study of Cognitive Aging (WHISCA)**
  The WHISCA project is an ancillary project of the Women's Health Initiative Memory Study and the Women's Health Initiative (WHI), a randomized clinical trial of hormonal therapy. Since 1999, WHISCA has investigated the effects of hormonal therapy on longitudinal changes in memory and specific cognitive functions in older, non-demented WHI participants.

The NIA supported several workshops on women's health-related topics in 2003 and 2004. In addition, the NIA is currently supporting an extensive program of research pertaining to health disparities among special populations; much of this research is relevant to the health concerns of minority women.

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. In 2003, women accounted for 58 percent of the population age 65 and over and for 69 percent of the population age 85 and over. Despite living longer, however, older women are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), are institutionalized earlier than men, and live in poverty at a disproportionately high rate.

The NIA supports a diverse portfolio of research on older women's health, including studies on: Alzheimer's disease and other types of dementia; menopause and hormone therapy; osteoporosis and age-related muscle loss; physical disability; caregiver burden (research has shown that care givers are more likely to be women); decline in function of older women; hip fractures; and cancer in older women.

A Women's Health Coordinator in the Office of Planning, Analysis, and Evaluation coordinates NIA activities related to women's health. Recent accomplishments in women's health, as well as ongoing and planned research initiatives aimed at women, are described below.

Accomplishments

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia among people age 65 and older, and is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. People with Alzheimer's disease gradually suffer memory loss and a decline in thinking abilities, as well as major personality changes. These losses in cognitive function are accompanied by pathologic changes in the brain, including the buildup of insoluble protein deposits, called amyloid plaques, and the development of neurofibrillary tangles, which are abnormal collections of twisted protein threads found inside nerve cells. Such changes result in death of brain cells and breakdown of the connections between them. AD advances gradually but inexorably, from early, mild forgetfulness to a severe loss of mental function called dementia. Eventually, people with AD become dependent on others for every aspect of their care.

Scientists now estimate that as many as 4.5 million people currently suffer with the disease, and this number is expected to increase to 13.2 million persons by 2050, an almost threefold increase. Currently, nearly half of all Americans ages 85 and older have AD. Risk of developing AD at any specific age is similar for women and men; however, because women live longer, there are significantly more women than men with AD, and in a recent epidemiological study, the overall lifetime risk of developing AD for a woman was nearly twice that for a man (32 vs. 18 percent).

Hormone Therapy and Alzheimer's Disease

Some previous studies have suggested that postmenopausal women using hormone therapy may have a reduced risk of developing cognitive decline. However, results from the Women's Health Initiative Memory Study (WHIMS), a substudy of the Women's Health Initiative, contradict these previous findings. In 2003, researchers found that women ages 65 and older taking Prempro™, a particular form of estrogen plus progestin hormone therapy, had twice the rate of dementia, including AD, compared with women who did not take the medication. The study also found that the combination therapy did not protect against the development of mild cognitive impairment, or MCI, a form of cognitive decline less severe than dementia. Furthermore, in 2004, researchers on the same study found that older

women using estrogen-alone hormone therapy could be at a slightly greater risk of developing dementia, including AD, than women who do not use any menopausal hormone therapy. The scientists also found that estrogen alone did not prevent cognitive decline in these older women.

Because of these findings, as well as findings suggesting that women on either hormone regimen were at increased risk of cardiovascular events, both arms of the trial were halted—estrogen/progestin in 2002 and estrogen alone in 2004.

However, the risks and benefits of hormone therapy remain under study. A new and related avenue of inquiry is the use of selective estrogen receptor modulators (SERMs) to prevent cognitive decline. SERMs mimic estrogen's actions in some tissues but block the action of the body's naturally occurring estrogen in others, offering the benefits of traditional hormone therapy with fewer potential health risks. In a recent study, the SERM raloxifene (Evista®), frequently prescribed for the prevention and treatment of osteoporosis, appeared to reduce the risk of cognitive impairment in postmenopausal women. Further studies are needed, but this is a promising area of research.

Diabetes and Decline in Cognitive Function

Diabetes mellitus (DM) affects about one in five persons over age 60 years, and has been associated with a variety of adverse health effects. Recently, four large-scale studies—the Religious Orders Study (ROS), the Nurses' Health Study (NHS), the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial, and the Rancho Bernardo Study (RBS)—linked DM to changes in cognitive function. The studies suggested the following: women with DM have an increased risk of developing substantial cognitive decline (NHS, MORE Trial, RBS); postmenopausal women whose blood glucose levels are elevated, but not yet in the "diabetic" range, i.e., "pre-diabetic," are also at risk for significant cognitive impairment (MORE Trial); and oral hypoglycemic agents may ameliorate the increased risk in women (NHS, RBS). One study (ROS) suggested that men and women with DM have an increased risk of developing AD, and that, for both sexes, DM affects different cognitive systems differently. Together, these results indicate that a successful public-health prevention strategy for DM may also have major consequences for preventing or delaying AD. They further suggest that patients with DM who receive treatment for their condition may receive some protection from cognitive decline.

Care Giving of Alzheimer's Disease Patients

Most of the over four million Americans with AD today are cared for outside the institutional setting by an adult child or in-law, a spouse, another relative, or a friend. Care givers—who are most often women—frequently experience significant emotional stress, physical strain, and financial burdens, yet they often do not receive adequate support. NIA's major caregiving program activity is the REACH project, begun in 1995 as six related but independent pilot studies of interventions to reduce caregiver depression and burden. Recompeted in 2001 as REACH II, with co-funding through the National Institute of Nursing Research, this multi-site randomized trial tests interventions to reduce depression and burden. Data collection ended in September and analysis of REACH II results is ongoing.

Sustained benefit of supportive intervention for depressive symptoms in care givers of AD patients. Family care givers of relatives with Alzheimer's disease are at high risk for psychological distress, particularly clinical depression. This risk persists over the many years of caregiving and even after caregiving ends with the death of the care recipient. Investigators followed 406 participants in the NYU Spouse-Caregiver Intervention Study, a long-running study of an intervention for family care givers of people with AD. Half of the spouse care givers received an initial period of intensive counseling, attended weekly support groups, and were encouraged on an ongoing basis to contact counselors for support. The second group of spouses was assigned to receive the "usual" support services for families of AD patients at the center, which included information about resources and advice upon request, but no formal counseling.

When they began the study, the two groups showed comparable levels of depressive symptoms, but after 1 year, 29.8 percent of care givers in the enhanced treatment group had symptoms of clinical depression compared

with 45.1 percent of those in the usual care group. Significant differences between the two groups were found through the third year of followup. These results offer evidence that distress and depressive symptoms in family care givers can be effectively eased and that the benefits can be sustained over a long period of time.

Long-term Care Placement of Dementia Patients and Caregiver Health and Well Being

In a recent study of the transition experience care givers undergo when institutionalizing a relative, investigators found that race/ethnicity, caregiver burden, and global cognitive function of the patient were important predictors of institutionalization. They also found that care givers who reported that providing help to their relative made them feel more useful, needed, appreciated, and important were less likely to institutionalize the patient. After the patient was institutionalized, half of spouse care givers and one-quarter of nonspouse care givers reported visiting the care recipient at least once a day, and nearly all reported visiting at east once a week. Spouses reported higher levels of depression, both before and after placement, and more anxiety after placement than non-spouse care givers. These findings suggest that although care giver bereavement studies have shown that care givers demonstrate recovery in response to the death of their loved one, the benefits to the care giver of institutionalizing the relative appear to be less positive, possibly because the caregiving role is not wholly relinquished after institutionalization.

Osteoporosis

It is estimated that over 10 million men and women currently have osteoporosis and an additional 18 million have low bone mass and are at risk. Treatment options for women have most often included hormone replacement therapy involving estrogen; however, recent clinical evidence has indicated that estrogen replacement therapy may have undesired side effects on other organs.

A newly defined pathway for steroid action on cells provides the means to reverse osteoporosis in mice. Researchers have identified a previously unrecognized pathway for estrogen action through a receptor at the cell surface, with subsequent steps to influence a set of genes in the nucleus that had not been known to be involved with estrogen action. They further found that this pathway of action is also used by androgen receptors and that a synthetic compound, 4-estren-3,17-diol, can activate both estrogen and androgen receptor pathways. Finally, studies in both male and female mice demonstrate that this mechanism of action can be used not only to preserve bone in animals lacking estrogen, but also to increase bone mass without stimulating unwanted effects in reproductive organs. This work has already had far-reaching effects in bone and steroid biology and provides an entirely new pathway for future clinical investigation to not only stop progression of bone loss, but reverse bone loss without dangerous side effects.

Newly Discovered Action of Hormone that Inhibits Bone Turnover and Net Loss of Bone

Under normal circumstances, bone renews itself constantly with specialized cells, called osteoclasts, resorbing old bone and osteoblasts creating new bone. The actions of osteoblasts and osteoclasts are tightly linked, but when this process goes awry, the amount of resorption is no longer in balance with the amount of bone made, and osteoporosis often results. In a recent mouse study, researchers found that reduction of thyroid stimulating hormone (TSH), which is made by the pituitary and stimulates production of thyroid hormones, inhibits osteoclast formation and survival, and also inhibits osteoblast differentiation. Although both osteoclast and osteoblast activities were impeded, the new result was a severe net loss of bone and severe osteoporosis. This is the first time that TSH has been shown to have control over both bone formation and resorption, independent of its action on thyroid hormone production. These results open an entirely new direction in investigation into understanding osteoporosis and how bone formation and resorption are coupled to maintain strong bone. It also helps to explain osteoporosis associated with hyperthyroid, which results in lower levels of TSH release via negative feedback to the hypothalamus and pituitary.

Elevated levels of homocysteine may be an important but modifiable risk factor for osteoporosis. In a recent study, investigators found a significantly greater risk of hip fracture for both men and women with high homocysteine levels compared to those with low levels. Because homocysteine levels can be modified by diets or vitamin supplements with sufficient levels of vitamins, such as folic acid, B6, and B12, such dietary strategies could reduce the burden of hip fractures in older individuals.

Reproductive Health and Menopause

Adult Mice Continue to Produce Eggs

One of the basic underpinnings of reproductive biology has been the tenet that the number of oocytes (eggs) in the ovaries of most mammals—including human women—is fixed at birth and declines throughout life, coinciding with a woman's diminishing fertility as she approaches menopause. However, NIH-supported researchers have recently uncovered surprising evidence that egg production in mice may continue throughout life. While additional research is needed, the results of this study have called into question decades of scientific thought. The finding that new eggs are produced into adulthood in mice may, if extended to human women, lead to interventions to regulate the rate at which oocytes are formed. This could, in turn, have important implications on the treatment of premature ovarian failure, the extension of fertility, or even the timing of menopause.

Age-associated Alteration of Gene Expression Patterns in Mmouse Oocytes

Reproductive capacity in women declines dramatically beyond the mid-30s, in part due to the decline in the quality of a woman's oocytes (eggs) as she ages. However, the molecular factors determining oocyte quality are poorly understood. NIA researchers have recently compared gene expression in oocytes collected from 5- to 6-week-old mice with those collected from 42- to 45-week-old mice (equivalent to late 30s in human). They found that about 5 percent of the genes profiled a variety of expression changes, including changes in genes associated with mitochondria and oxidative stress. These provide important insights into the mechanism of oocyte aging as well as the potentially important implications for the safety and efficacy of egg donation.

Foxl2 Deficiency Causes Mouse Ovarian Failure by Pervasive Blockage of Follicle Development

Premature ovarian failure (POF) is a common condition, affecting 1 to 3 percent of all women, in which early menopause could result from inadequate formation or maintenance of the pool of ovarian follicles. Researchers recently determined that in mice, POF can arise from disrupted follicle development, with the Foxl2 gene as a selective determinant of perinatal ovarian development. Foxl2 disruption in mice provides the first model directly relevant to POF in humans, along with a route to genes selectively involved in the determination of the critical follicle pool. Such genes should include candidates for mutation in other instances of POF, where affected genes have been difficult to identify. In the long run, they may provide targets for therapeutic intervention.

Late childbearing is associated with healthy longevity at the oldest ages. Women in advanced industrialized countries are increasingly delaying childbearing into their late 30s and 40s. While extensive research has examined the risk associated with doing so for children, less research has addressed the consequences for mothers and even less has focused on the long-term consequences of late childbearing. In a recent study, researchers demonstrated that late childbearing (defined as after age 35 or 40) is significantly associated with survival and healthy survival (of the parent) among oldest-old Chinese women and men. Although this association exists among oldest-old women and men, the effects are substantially stronger in women than in men. While the mechanism behind this phenomenon has yet to be determined, and the findings here are limited to China, this study suggests that there may be positive long-term consequences for women of having children in their late 30s and 40s.

Decreased Sensitivity to Estrogen May Help Explain Menopausal Changes

A new study suggests that age-related changes in how the brain responds to the female sex hormone estrogen may be involved in a woman's transition through menopause. The study provides new clues about hormonal influences

on hot flashes and night sweats experienced by some women in the menopause transition.

A New Rodent Model of the Menopause

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

Possible New Mechanism for Hot Flashes

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

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

The Menopause Transition and Depression

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

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

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

- Serum E2 concentrations decreased significantly with age, with a steeper decline at higher ages.

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

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

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

Other Research Accomplishments

Importance of Walking for Maintaining Mobility

In a recent study of community-dwelling women enrolled in the Women's Health and Aging Study, investigators found that functionally limited women, ages 65 and older, who walked at least eight blocks per week outside their homes, were better able to maintain their functional capacity and walking ability than women who walked less or did not get out the door at all. This effect is independent of initial functional capacity, disease profile, health-related behaviors, and psychological and social-demographic factors. These results provide strong evidence that even a small amount of regular walking can help to maintain mobility.

Reducing the risk of diabetes may require different strategies in women of different race/ethnicities. With respect to changes in glucose metabolism, the primary problem in African American women may be decreased insulin sensitivity; whereas those in Asian women may be both decreased insulin sensitivity and reduced β-cell function in the pancreas.

A Mechanism for Drug Resistance in Ovarian Cancer Cells

Cisplatin is a commonly-used chemotherapy for ovarian cancer; however, cancer cells frequently develop resistance to cisplatin-based therapy. Researchers recently demonstrated that tumor cells can remodel their microenvironment through production of the protein collagen VI and that the presence of collagen VI increases resistance of ovarian cells to chemotherapeutic agents. These findings may lead to the identification of novel avenues for treatment of drug-resistant tumors.

Behavioral Training with and without Biofeedback in the Treatment of Urge Incontinence in Older Women: A Randomized Controlled Trial

Urge urinary incontinence (inability to delay voiding until one can reach a toilet) is a common condition that affects millions, especially older women. Research, including controlled trials, has shown that various behavioral training techniques and biofeedback regimens are safe and effective treatment for this condition as an alternative to drug treatment. However, little is known about whether biofeedback, which can be both expensive and invasive, provides additional benefits beyond those of behavioral training. In a randomized clinical trial of 222 non-institutionalized women, ages 55 to 92, researchers compared the effects of biofeedback combined with other behavioral training, with the effects of two other behavioral interventions—verbal feedback and a self-help program—in helping the patients identify their pelvic floor muscles to prevent urge incontinence episodes. All interventions were conducted for 8 weeks. The frequency of incontinence was reduced in all three treatment groups. Biofeedback did not have greater efficacy than the other two interventions. The results of this study have considerable public health importance in that they indicate that behavioral training, a non-invasive, inexpensive treatment that does not require specialized equipment, can be used to effectively treat urge incontinence.

Role of Insulin-like Growth Factor I and Interleukin-6 on Health Outcomes in Older Disabled Women

There has been increasing interest in the role of deficits in growth factors and elevations in inflammatory factors in disease, disability, and mortality in the elderly. The identification of physiological markers of these abnormalities may be useful in identifying those persons at higher risk for poor outcomes, and for identifying possible preventive or treatment interventions.

Researchers recently explored the association between age-related functional decline (including death) and the effects of changes in both insulin-like growth factor I (IGF-I; a hormone) and interleukin-6 (IL-6; a pro-inflammatory factor) in disabled older women. Older women with low IGF-I levels and high IL-6 levels had significantly greater limitation in walking and disability in mobility tasks and activities of daily living than those with neither risk factor. The combination of low IGF-1 and high IL-6 was associated with far worse outcomes than was either individual abnormality. The combination of the two produced a more-than-additive effect. Older women with both risk factors (low IGF-I and high IL-6 levels) were at tenfold greater risk for walking limitations, and more than double the risk for disability in activities of daily living, compared with older women with high IGF-I and low IL-6 levels. At 5 years of follow up, 46 percent of the women assessed with both low IGF-I and high IL-6 were dead, compared with only 23 percent of older women with both high IGF-I and low IL-6 levels.

Initiatives

Program Announcements (PA)

- **Biology of the Menopausal Process and Associated Health Conditions During and After Menopause**
  This March 2001 PA addresses: 1) the underlying biology of age- and menopause-related changes in the hypothalamic-pituitary-ovarian axis that result in the dramatic hormonal changes experienced across the menopausal transition; and 2) how the biology of menopause impacts

the menopause-related increase in health problems and conditions associated with the brain, cardiovascular, skeletal, genitourinary, and other physiologic systems.

Conferences and Workshops

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

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

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

  – To define and examine the discrepancies between the findings of the Women's Health Initiative/Women's Health Initiative Memory Study on brain and cognitive function and the basic and longitudinal/epidemiological studies;

  – To examine the effects of estrogens on brain and cognitive function as they relate to aging;

  – To determine what is known and what information we would need to obtain that would determine whether additional hormone "interventions" could be developed; and

  – To determine what lessons we have learned from studies on estrogen that will help in designing clinical trials for other classes of drugs.

  This workshop brought together a wide range of experts who have studied estrogen from basic science, reproductive epidemiology, clinical studies, and clinical trials. A number of NIA-supported investigators, and the NIA and the NIH/DHHS staff participated. The workshop was co-sponsored by ORWH, NIMH, and the Alzheimer's Association. The meeting agenda, abstracts, list of participants, summaries of cognitive function studies, and Power Point presentations can be viewed at the meetings listing under the NNA program of the NIA website (*http://www.nia.nih.gov/*). Key discussion points and outcomes of the meeting are presented here.

- **Aging, Vascular Calcification and Bone Mass The Tenth Annual Meeting of the Working Group on Aging and the Human Skeleton**
  Objectives of this October 4, 2004 workshop were to review the current state of knowledge and address methodological issues integral to facilitating clinically relevant studies on the causes and

consequences of bone loss and osteoporosis as it occurs at the cellular and tissue levels in adult and elderly humans. This working group was organized by staff from the NIA, the NIDR, and the St. Joseph's Hospital, Bangor, Maine.

Ongoing Research Initiatives

Study of Women's Health Across the Nation (SWAN), an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to postmenopause is of high relevance to understanding healthy aging in midlife women and beyond. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in Caucasian, African American, Chinese, Japanese, and Hispanic women. Funded initially in September 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center (CC), an advisory panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health. Ancillary studies are supported by the NNA/NIA, the NIMH, the NHLBI, and the National Center for Complementary and Alternative Medicine.

- **The Women's Health Initiative Study of Cognitive Aging (WHISCA)**
  The WHISCA project is an ancillary project of the Women's Health Initiative Memory Study and the Women's Health Initiative (WHI), a randomized clinical trial of hormonal therapy. Since 1999, the WHISCA has investigated the effects of hormonal therapy on longitudinal changes in memory and specific cognitive functions in older non-demented WHI participants. Preliminary findings on the 2,300 participants suggest that hormonal therapy may have both beneficial and deleterious effects on specific cognitive functions. Future plans for this study include testing the hypotheses that beneficial effects of hormone therapy on age-related changes in cognitive function are associated with preservation of brain volume, and that decline in cognitive function will be associated with cerebral microvascular change and/or subclinical cerebral infarcts.

- **Endogenous Sodium Pump Ligands as Targets for Therapy in Preeclampsia**
  Preeclampsia complicates about 10 percent of pregnancies worldwide and remains the leading cause of maternal and fetal morbidity and mortality. There are several theories for the cause of the condition. For example, blood levels increase throughout pregnancy, and previous studies have demonstrated that increased levels of endogenous sodium pump ligands (SPLs) facilitate excretion of sodium and fluids. However, when this mechanism goes awry, vasoconstriction and dangerously increased blood pressure can result. Research at the NIA is ongoing to elucidate the physiological roles of SPL in normal pregnancy and to develop treatments for preeclampsia based on increased understanding of SPL.

Planned Activities

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

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

Health Disparities among Special Populations of Women

The health status of racial and ethnic minority groups in the United States has improved steadily over the last century. Despite this progress, disturbing disparities in health persist between majority and minority populations. Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. Research to date has shown that health disparities are associated with a broad, complex, and interrelated array of factors. Disease risk, diagnosis, progression, response to treatment, caregiving, access to care, and overall quality of life each may be affected by variables such as race, ethnicity, gender, socioeconomic status, age, education, occupation, country of origin, and possibly other lifetime and lifestyle differences.

The NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Center on Minority Health and Health Disparities. Minority aging research is conducted throughout the Institute's programs, and much of this research has relevance to the health needs of minority women. Examples of current programs and projects include:

- An ongoing study to examine perceptions of mistreated elders, as well as care givers, healthcare providers, and adult protective service workers, with regard to elder abuse and mistreatment; identify risk factors for elder abuse; and begin development of a screening tool for use in healthcare settings.
- The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations.
- A new year-long project, Promoting Research Participation among Black and Hispanic Seniors, will: 1) explore ongoing and completed Yale–Older Americans Independence Center recruitment and retention data to identify characteristics of Black and Hispanic study participants and non-participants; 2) interview key informants with intimate knowledge about ways to promote research participation among the targeted samples; and 3) conduct focus group discussions on the topic of recruitment and retention of minority older adults into aging-related research among representatives of the type of Black and Hispanic older adults participants likely to be targeted by studies of multi-factorial geriatric health conditions.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

There is no single specific position or component within the National Institute on Alcohol Abuse and Alcoholism (NIAAA) designated for research on women's health, instead each division, office, and team addresses these issues. The following items include significant sex and gender studies funded during fiscal years 2003 and 2004: health disparities and special populations of women including rural women. The following reports include contributions from the Divisions of Epidemiology and Recovery Research, Neuroscience and Behavior, Metabolism and Health Effects, and Treatment and Prevention Research. In 2004, the NIAAA had two grants funded by the ORWH through the REAP award program. The NIAAA also participated in the 2004 Request for Applications for BIRCWH.

Accomplishments

Psychosocial Determinants of Drinking in Women

Victimization and Childhood Physical Abuse

A study of rural women in the United States revealed that victimization is a risk factor for alcohol and other drugs (AOD) disorders in this population, and women with AOD disorders experience greater stress and fewer positive events, in addition to having fewer resources for coping with problems. Another study which examined the role of physical abuse in childhood and long-term health consequences found that although more boys than girls

experience physical abuse, the experience is generally more detrimental for girls than for boys.

Sexual Identity and Drinking

A study of college students found that sexual identity is an important predictor of AOD use and that while alcohol use did not differ between lesbian and heterosexual women, lesbian women were more likely to experience certain AOD-related consequences—smoke cigarettes and use marijuana, ecstasy, and other drugs.

Prevalence of Alcohol Dependence and Birth Cohort

A large scale epidemiologic analysis revealed a 1.8 percent lifetime rate of DSM-III-R alcohol dependence in women born before 1940 as compared to a rate of 13 percent in women born after 1960. (The results were 15 and 28 percent, respectively, for men.)

Violence and Other Social Consequences of Alcohol Misuse

Alcohol and Partner Violence

Although cross-sectional studies have revealed an association between women's substance use and intimate partner violence, a recent longitudinal study found that women's heavy episodic drinking did not predict subsequent experiences of intimate partner violence in ongoing or new relationships. Another recent analysis indicated that among newly-wed couples that experience husband-to-wife violence, those violent episodes in which the husband was drinking included more acts of violence, more severe violence, and more aggressive behavior among the wives.

Alcohol and Sexual Assault

A study of the bar context and victimization revealed, not unexpectedly, that certain environmental characteristics, such as a greater proportion of young patrons and pool playing, as well as social behaviors, such as level of alcohol consumption and leaving the bar with strangers, are associated with more severe bar-related aggression experienced by women. A timeline follow-back study, examining the temporal relationship between victimization and alcohol consumption in a sample of college women, found that the odds of experiencing sexual and nonsexual aggression were nine and seven times higher, respectively, on heavy drinking days, and three times higher on nonheavy drinking days as opposed to nondrinking days. A study comparing forcible rape and incapacitated rape found nearly identical lifetime prevalence of these occurrences, with about one in ten women reporting each type of rape subsequent to age 14. Age and childhood sexual abuse predicted forcible, but not incapacitated, rape while adolescent alcohol and drug use predicted incapacitated, but not forcible, rape. Results of another analysis from the same study show that perpetrator intoxication at high levels impairs male sexual function, but increases physical aggression, and that victim intoxication increases vulnerability to penetration.

Alcohol and Suicide among Women

A longitudinal analysis of the long-term antecedents of suicidal ideation among women in the United States general population revealed that such ideation is largely predictable from prior suicidal ideation, hazardous drinking, adverse childhood experiences, and domestic stressors.

Violence and Women in the Military

A cross-sectional survey of women veterans revealed that repeated exposure to intentional violence is a relatively common experience among women in the military. Women who experience repeated violence during their military service had poorer health outcomes and more often reported a history of childhood and post-military violence.

Alcohol Impairment of Behavior in Men and Women

Studies have shown that alcohol impairs the ability to inhibit behavioral responses in humans and some evidence suggests that men might display greater impairment than women. The present study compared men and women in the degree to which a moderate dose of alcohol impaired their inhibitory control at comparable blood alcohol concentrations. Twelve male and 12 female adult social drinkers received a moderate dose of alcohol (0.65 g/kg) and a placebo in a counter-balanced order and performed a cued go/no-go task that measured the ability to inhibit and execute behavioral

responses. When the behavioral response was instigated, men displayed greater impairment of inhibitory control under alcohol than women. Men also reported greater levels of subjective stimulation from alcohol compared with women, who reported more sedation from the drug. Gender difference in alcohol impairment of inhibitory control could account for observations that disinhibited and aggressive behaviors under alcohol are more pronounced in men than in women. Gender difference in alcohol impairment of inhibitory control could account for observations that disinhibited and aggressive behaviors under alcohol are more pronounced in men than in women.

Impact of Alcohol Use and Misuse on Women's Physiology

Gender differences in body composition and in the metabolism of alcohol are important to consider when evaluating the health effects of drinking by women since such differences may result in gender-specific consequences for women, for both drinking in general and for specific patterns of consumption.

Alcohol Use and Physical Health Outcomes

Ongoing analyses of the Nurses' Health Study, a prospective longitudinal study of substantial size, continue to reveal interesting findings about the relationship of alcohol consumption over many years and various health-related outcomes. Recent findings indicated that: moderate alcohol consumption had no substantial adverse effect on renal function in women during 11 years of followup; moderate alcohol consumption (one to two drinks/day) may have a beneficial glycemic effect, particularly among overweight women; light to moderate consumption may be associated with a lower risk of type 2 diabetes mellitus among women aged 25 to 42, although consumption at higher levels may not confer this benefit; and consumption of any type of alcohol beverage was inversely associated with cholecystectomy risk, independent of consumption patterns. In another analysis of data from this study, researchers examined the association of alcohol and folate intake with the risk of major chronic disease. They found a positive association between heavy alcohol and low folate intake, indicating the possibility that adequate folate intake may be important in the primary prevention of overall major chronic disease in women, especially among younger women who consume more than two drinks per day.

A study comparing women in Iowa, aged 18 to 70, who were in treatment for alcohol abuse, who were in recovery and abstaining from alcohol, and who had no history of alcohol abuse, found that women in treatment and recovery reported more fractures in childhood and early adolescence than control women, that women in recovery reported more fractures following sobriety than control women, and that alcohol abuse and dependence was associated with lower femoral neck and lumbar spine bone mineral density.

Estrogen Modulation of Immunity with Ethanol and Burn Injury

Studies have shown that ethanol consumption is a causative factor in the occurrence of burn or other traumatic injuries. It has also been shown that individuals who sustain injury under the influence of ethanol suffer increased morbidity and mortality compared to others. Many of the complications seen with ethanol-exposed, burn injured individuals result from depressed immune responses that render the person more susceptible to infectious organisms. Both ethanol and injury independently affect cellular immune responses, and ethanol and injury in combination increase the magnitude and duration of the immunosuppression seen. Research has shown that the immune response can be restored in males but not females given a proestrous levels of estrogen. It seems that the combined insult of ethanol and injury on the level of gonadal steroid hormones produced has an effect on cytokine gene expression in sensitive cell types, like macrophages. Evidence suggests that cellular immune responses after ethanol and burn injury differ in magnitude and kinetics for male and female subjects suggesting that sex be a factor in the determination of therapeutic interventions to treat burn injured patients.

Leutinizing Hormone Secretion is Altered by Alcohol in Immature Female Rhesus Monkeys—A Hypothalamic Mechanism

Although case studies of alcohol use by adolescent and teenage humans have been limited in number and scope, they suggest that alcohol

can disrupt endocrine function, stature, and weight distribution in young people. Previous studies have shown that alcohol administration inhibits the secretion of puberty-related hormones and delays development of a normal pattern of menstruation in a developing female rhesus monkey animal model. Researchers now extend their observations in an attempt to dissect whether the suppression of leutinizing hormone (LH) release by alcohol has a purely hypothalamic or pituitary site of action. From 20 months onward to 36 months, animals received a single intragastric dose of alcohol and controls and equal volume of saline/sucrose. The pituitary challenge revealed that LH-releasing hormone (LHRH) stimulated LH release in control and alcohol-treated animals equally. In contrast, the hypothalamic challenge showed that N-methyl-D-L-aspartic acid stimulated release from LH release from the control but not from the alcohol-treated animals.

Alcohol, Estrogen Replacement Therapy, and Visuospatial Processes in Postmenopausal Women

Some studies suggest that moderate drinking may benefit cognition and the effect may favor women. This study investigated effects of moderate drinking on visuospatial functioning in postmenopausal women. Visuospatial processes are sensitive to alcohol abuse and are thought to be sensitive to hormonal fluctuations. Three questions were posed in order to: explore visuospatial processes in moderate-drinking and abstaining postmenopausal women; assess visuospatial differences in women using no estrogen replacement therapy (No-ERT), ERT alone (ERT-only), and ERT with progestin (ERT+Pro); and identify alcohol/ERT interactions associated with visuospatial performance. The data generated suggest that moderate drinking may be positively associated with visuospatial processes in postmenopausal women. They also suggest that ERT, alone and with progestin, is positively associated with visuospatial processes, but only when the task is difficult. These findings support Kaplan's assertion that subtle performance deficits may not be detectible with traditional endpoint measures. A provocative alcohol x ERT trend suggests that alcohol consumption should be considered in studies of ERT effects on cognitive ability.

Auditory P3 in Female Alcoholics

The P3 (P300), an electrophysiological measure of brain function, has been considered to be a phenotypical marker of the risk for alcoholism.

Although reductions in visual P3 in male and female alcoholics have been replicated, studies of auditory target P3 have been inconsistent. The objective of this study was to assess the magnitude of auditory P3 reduction in female alcoholics and to establish the association between P3 reduction and alcoholism, while taking into account co-morbid depression and psychoactive drug dependence. The characteristics of P3 reduction were further examined by studying the reduction in family history-positive and -negative individuals. Alcoholic women had significantly lower P3 amplitudes. The reductions were not associated with co-morbid depression, as shown by low correlations and similar P3 amplitudes at Pz in female alcoholics with and without depression. The P3 amplitudes in women with a high family density were smaller than those in women with a low family density of alcohol dependence. Drug dependency did not influence P3 amplitude, as shown by similar responses in drug-dependent and non-drug-dependent alcoholic women. These findings highlight the significance of P3 reductions associated with alcoholism in women, independently of co-morbid depression. Family density effects further support the evidence that these findings are heritable. These results suggest that P3 can be considered as a phenotypic marker of vulnerability to alcoholism in women.

Drinking during Pregnancy

Studying the long-term developmental consequences for children exposed to maternal alcohol use during pregnancy continues in two prospective longitudinal studies, one in its 18th and another in its 29th year. These studies continue to uncover adverse consequences of low to moderate levels of prenatal exposure. Exposure to alcohol during the first and second trimesters was found to be associated with poorer teacher ratings of overall school performance, and second trimester binge drinking was found to be associated with lower reading scores. Other recent analyses indicate that prenatal exposure continues to affect size at age 14,

although children who grow up in more affluent circumstances are likely to make up their early growth deficits. In a third study of shorter duration which followed the offspring of pregnant teenagers, prenatal alcohol was again shown to be associated with growth deficits. In an analysis of data from the longest-term study, prenatal alcohol exposure was found to be associated with alcohol problems at 21 years of age.

Screening, Intervention, and Awareness of Risk of Drinking during Pregnancy

Given the large body of evidence for negative outcomes as a result of prenatal alcohol exposure, screening and intervention among pregnant women is clearly important. A recent study of low-income minority women underscored the importance of screening in this population and indicated that among Hispanic women, those more acculturated to the United States tended to incorporate the drinking patterns of the larger U.S. population more than less acculturated women did. Another study demonstrated the feasibility of screening in large, busy obstetric clinics and the value of targeting smoking women who are also more likely to drink. A third study underscored the importance of screening and referring pregnant women for depression during this vulnerable time, since addressing this depression will likely ameliorate the risk of these women consuming alcohol during pregnancy.

Finally although we may assume that all women are aware of the potential negative outcomes associated with drinking during pregnancy, this is not the case. A study in a rural community indicated that neither men nor women were knowledgeable about the harmful effects of alcohol use during pregnancy and that barriers to treatment of women with alcohol problems in such communities include the lack of available and accessible treatment for women referred to treatment.

One of the most serious consequences of prenatal alcohol is the delivery of a child with fetal alcohol syndrome (FAS). A comparison of high-risk women in South African and among U.S. Plains Indians indicates less detectable damage among the U.S. Indian than among the South African sample, although both groups report similarly high levels of binge consumption. It is hypothesized that body mass index and lifelong and current nutrition may have an important impact on the relative risk of an FAS birth.

Is maternal alcohol use a risk factor for early-onset sepsis in premature newborns? Chronic alcohol abuse alters immune defenses and increases infection in adults. The question posed was whether women who drink during pregnancy would increase the risk of sepsis in very-low-birth-weight (VLBW) premature newborns. A case controlled analysis of VLBW newborns was performed and alcohol exposure as a predictive variable was assessed by maternal self report. The outcome variables were early-onset and multiple late-onset sepsis. Early-onset sepsis was 15-fold higher in the alcohol-exposed group compared with findings for the matched-control group. The prevalence of late-onset sepsis did not differ among the exposure groups. Alcohol exposure greatly increased the risk of early-onset sepsis in a group of very-low-birth-weight newborns. Further studies are needed to more thoroughly examine the effects of alcohol abuse during pregnancy on the risk of infection in VLBW newborns.

Treatment of Women with Alcohol Use Disorders

Treatment Efficacy

Several studies compared the effectiveness of certain treatments for women as compared to men. One such study indicated that while choice of treatment modality varied by sex, effectiveness did not, once other explanatory variables were accounted for. Another study examined gender differences in treatment outcomes and predictors of outcome among men and women in a gender-sensitive substance abuse program. Those researchers found that outcomes for men were predicted primarily by mental health and medical problems, substance abuse problem severity, and whether or not they completed treatment; and for women by treatment completion and social, sociodemographic, and life-history characteristics. Women who completed treatment were nine times as likely as non-completers to be abstinent at 7 months; male completers, on the other hand, were only three times as likely as non-completers to be abstinent.

Healthcare Utilization

A study of female healthcare workers indicated no difference in total, outpatient, or inpatient costs between moderate drinkers and abstainers/light drinkers, but found that pharmacy costs were significantly lower for moderate drinkers than for abstainers/light drinkers.

Alcohol Treatment and Couples Therapy

A study which examined partner violence before and after behavioral couple's therapy (BCT), for couples in which the male partner was an alcoholic patient, found a decreased violence after BCT, particularly in the context of reduced problem drinking and remission of alcoholism. Another analysis found that the majority of alcohol-dependent clients and partners reported that the non-alcoholic partner took over responsibilities from the alcoholic client, drank or used drugs with the client, and lied or made up excuses to others to cover up for the drinking partner, indicating the need for involving partners in treatment.

Project MATCH: Matching Alcoholism Treatments to Client Heterogeneity

Gender analyses from Project MATCH found a more rapid rate of progression of alcoholism (i.e., more rapid course and appearance of alcohol dependence symptoms) among women compared to men, similar to findings from other studies. In addition, there was a much higher prevalence of physical, emotional, and sexual abuse among females in our treatment-seeking population than among men, again consistent with other smaller studies.

Reducing Alcohol and Risks among Young Females

An ongoing intervention study will characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African American and Latina adolescent females who are at high risk for HIV/AIDS and other infections. Past research by the investigative team has documented that nearly 10 percent of females in their target population are at risk in 7th grade and more than half by spring of 10th grade. This study, involving parents and their 8th grade daughters, will examine the effectiveness of an audio-CD intervention in promoting attitudes and behaviors associated with reduced alcohol consumption and sexual risk taking among adolescent girls. The study will further examine whether changes in the girls' attitudes and behaviors are mediated by changes in certain parenting mechanisms, including parental monitoring, household rule setting, and communication. The study has the potential to improve understanding of the link between early alcohol and risky sexual behavior and to provide a proven, selective, female-focused intervention for addressing these risks.

Brief HIV and Alcohol Combined Interventions for Women

An ongoing randomized clinical trial is focusing on reducing HIV risk behaviors among women seeking help for alcohol problems. This study will evaluate the relative effectiveness of combined behavioral intervention (CBI), a state-of-the-art, empirically based treatment for addressing alcohol problems in dependent drinkers, followed by an HIV-risk reduction intervention (HIV-RR) and CBI followed by an intervention limited to dissemination of HIV information (HIV-I). The investigators predict that women who respond favorably to alcohol treatment and who receive the HIV-RR, an enhanced intervention including both HIV-related information and elements to increase motivation and behavioral skills necessary to reduce HIV-risk behavior, will fare better than their counterparts in HIV-I. It is anticipated that findings from this study will inform the development of future combined alcohol and HIV-risk reduction interventions.

Screening and Brief Intervention of Problem-drinking Women

Early identification and intervention among problem-drinking women may avert the more severe, adverse consequences of alcohol abuse and dependence. Among nonpregnant women of childbearing age, the use of alcohol and, in particular, the riskier practices of frequent and binge drinking, have not changed since 1995. An ongoing randomized trial is evaluating the effectiveness of screening and brief intervention (BI) in reducing risk drinking (exceeding NIAAA sensible-drinking limits of seven drinks per week or one to two drinks per episode) by nonpregnant women with three specific medical problems exacerbated by excessive alcohol consumption: diabetes, hypertension, and

infertility. The investigators predict that significantly more women who receive the medically oriented brief intervention than who receive medical treatment as usual will achieve NIAAA sensible-drinking limits in the 12 months following study enrollment. It is also anticipated that clinical outcomes related to the targeted medical conditions will be better among women who achieve NIAAA sensible-drinking limits. Findings from this study will inform future recommendations regarding alcohol screening and interventions in general medical settings.

Integrative Service for Substance-abusing Battered Women

There is little knowledge regarding the types of integrative services that have potential benefit for women with experiences of both intimate partner violence (IPV) and alcohol and other substance abuse problems, especially from the standpoint of the women themselves. In addition, little is known about the feasibility of incorporating integrative services for co-occurring IPV and alcohol and other substance dependence into existing addiction treatment programs and shelters for battered women. An ongoing study is examining the extent to which addiction treatment programs and shelters for battered women in one community have incorporated integrative services for co-occurring IPV and substance dependence into their treatment planning for women. In addition, it will generate additional and alternative ideas for incorporating integrative services into shelters and treatment programs where such services are not currently offered. Given the strong association between alcohol abuse/dependence and IPV and the negative impact of IPV on prospects for recovery, findings from research on integrative services may lead to improved treatment and better treatment outcomes among battered women with alcohol use disorders.

Community Reinforcement Approach and Enhance Job Training for Homeless Women

Women and families now comprise about 30 percent of the homeless population, and they are viewed as the fastest rising subgroup. Previous research indicates that alcoholism is the most common health problem among homeless women. An ongoing randomized clinical trial is evaluating the relative effectiveness of three approaches to treatment, including case management (CM), the community reinforcement approach (CRA), and an enhanced CRA program called Community Reinforcement, Employment, and Training Enhancement (CREATE), in reducing drinking and improving employment status and housing stability among homeless women with alcohol use disorders. While CRA, a behavioral intervention that focuses on linking individuals in addiction treatment to housing and other critical social services, has been proven to be effective in the treatment of alcoholism, a preliminary assessment of its effectiveness among women found that many women relapsed when both their treatment and their stay in the abstinence-contingent, free housing ended. The study also found a high rate of unemployment post-treatment. The current project includes an enhanced CRA component which provides aftercare, job training, and employment-oriented motivational interventions during the high-risk post-treatment period. Investigators anticipate that both of the CRA conditions will result in significant improvements in alcohol use, employment, and housing stability compared to CM, and that the enhanced CRA group will achieve better employment outcomes than the regular CRA group. Given that homeless women with alcohol use disorders (AUDs) historically have been among the most difficult groups to engage and retain in treatment, findings from this study could have important public health implications.

Biobehavioral Correlates of Alcohol Use and Misuse in Women

Alcohol intoxication induces greater reductions in brain metabolism in male than in female subjects. The mechanisms underlying the gender differences in alcohol drinking behavior and alcohol's effects are poorly understood and may reflect gender differences in brain neurochemistry. Alcohol decreases glucose metabolism in the human brain in a pattern that is consistent with its facilitation of GABAergic neurotransmission. The regional changes in brain glucose

metabolism were compared during alcohol intoxication in female and male subjects. Alcohol significantly and consistently decreased whole-brain metabolism. The magnitude of these changes was significantly larger in male than in female subjects. Half of the female subjects had reductions in metabolism during intoxication that were significantly lower than those in male subjects. This blunted response in the female subjects was not due to differences in alcohol concentration in plasma, because these did not differ between the genders. This study shows a markedly blunted sensitivity to the effects of acute alcohol on brain glucose metabolism in female subjects that may reflect gender differences in alcohol's modulation of GABAergic neurotransmission. The greater behavioral effects of alcohol in female subjects despite the blunted metabolic responses could reflect other effects of alcohol, for which the regional metabolic signal may be hidden within the large decrements in metabolism that occur during alcohol intoxication.

National Institute on Deafness and Other Communication Disorders

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. The NIDCD also conducts and supports research and research training that are related to disease prevention and health promotion.

The NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The institute supports efforts to create devices that substitute for lost and impaired sensory and communication functions. A number of diseases, disorders, or conditions within the mission of the NIDCD affect women disproportionately. Examples of significant research programs have been selected for inclusion in this report. Highlights of the latest research advances and plans for the future in these areas follow.

Accomplishments

Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of sensorineural hearing loss (SNHL) per year. NIDCD-sponsored scientists continue to make significant progress to fully characterize the effects of CMV on sensorineural hearing loss (SNHL) as well as the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on the development of late onset SNHL.

The NIDCD supports both basic and clinical studies to better understand the relationship between congenital CMV infection and hearing loss. NIDCD-supported investigators have developed an animal model (mouse) of congenital cytomegalovirus infection and are pursuing fundamental questions concerning disease pathogenesis. Human studies are aimed at the characterization of maternal CMV-status in an effort to determine the relationship between the type of maternal infection (recurrent or primary) and congenital CMV infection. This research is critical for fully determining the features in the natural history of maternal CMV infection and mother-to-child transmission that contribute to SNHL and late onset SNHL. Such studies are essential for the development of rational clinical approaches aimed at ameliorating CMV-induced congenital hearing loss.

In July 2003, the NIDCD released a Request for Proposals (RFP 260-03-18): The Natural History of CMV-related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing Screening in the Newborn. The goals of the solicitation for contract proposals were: 1) to correlate CMV status at birth with the presence of permanent/progressive sensorineural hearing loss, 2) to acquire data on the incidence, time course, and audiologic outcomes of CMV-related hearing loss, and 3) to determine the extent to which CMV screening

can improve detection and prediction of either existing or progressive hearing loss if combined with the metrics already in use for newborn hearing screening. As a result of this RFP announcement, three proposals were received and peer reviewed.

Hormonal Influences on Communication

For animals that breed seasonally, reproductive cycling is often coupled with changes in the sounds an animal makes to facilitate courtship and territoriality. Less is known about how those animals perceive the sounds made by a potential mate. NIDCD-supported studies in fish have shown that females treated in either testosterone or 17b-estradiol exhibit an increase in their ability to hear certain aspects of the male advertisement call; this auditory phenotype is nearly identical between steroid-treated nonproductive and wild caught reproductive females. Thus, the change in hearing is not a fixed trait, but rather steroid dependent. Similar mechanisms of auditory plasticity may also function in humans where cyclical changes in frequency sensitivity of females at differing stages of the menstrual cycle are dependent, in part, on the influences of steroids. Further studies may shed light on how sensory function changes with hormonal fluctuations.

Taste Perception

There are genetic and pathological variations in taste quality perception that affects the intensity of bitter foods and the preference for sweet and fat foods, which are important mediators of proper nutrition, cardiovascular disease, and cancer. Oral phantoms (sensations in the absence of stimulation) and oral pain (burning mouth syndrome) often accompany pathologies associated with the taste cranial nerves. Burning mouth syndrome occurs predominantly in postmenopausal women. NIDCD-funded research is exploring the dysfunctional relationships between the taste system and oral (trigeminal) pain systems in women with burning mouth syndrome, and will provide new insights into oral pain assessment and treatment.

Olfactory Loss in Multiple Sclerosis

Multiple sclerosis is the most common neurological disability in the young adult and is characterized by a progressive demyelination of axons in the central nervous system. A greater proportion of women than men with multiple sclerosis show olfactory loss and the loss is more profound in women. Olfactory loss has significant adverse dietary/nutrition consequences that impact on overall health status. NIDCD-funded research will define the nature of the olfactory dysfunction present in multiple sclerosis in women and will determine the relationship between the degree of olfactory deficit, cognitive function, and pathological alterations within specific central nervous system structures.

Gestational Diabetes and Altered Taste Sensitivity

Gestational diabetes is a common complication of pregnancy that requires special attention to diet to insure proper maternal and child health. NIDCD-funded research has shown that gestational diabetes can adversely affect nutrition by increasing the preference for, and intake of, sweet-tasting foods. Altered sweet sensitivity appears to be related to the blood levels of certain hormones and metabolites, and to a change in glucose tolerance that often accompanies pregnancy. The long-term goals of these studies are to better understand the various mechanisms underlying gestational diabetes, to isolate risk factors, and to develop better preventive and therapeutic dietary interventions.

Assessment and Treatment of Voice Disorders

Voice disorders effect millions of Americans, influencing their quality of lives and impairing their ability to communicate effectively and to function in our society. A number of voice disorders appear to effect women more frequently than men. The NIDCD currently supports a number of projects focused on normal and disordered voice processes. Of note are the studies examining behavioral vocal hyperfunction. Vocal hyperfunction is not organic

in origin, but rather a result of a habitual pattern of overuse, misuse, or possibly abuse of the vocal mechanism. A currently funded project is examining the vocal performance of teachers, a profession predominantly comprised of women. Research in the area of voice with representation of women should enhance our knowledge of this human ability and maximize laryngeal health and prevention of injury. Efforts to study voice restoration would minimize disabling effects and function and enhance quality of life.

National Institute on Drug Abuse

The National Institute on Drug Abuse (NIDA) supports over 85 percent of the world's research on the health aspects of drug abuse and addiction. The NIDA-supported science addresses the most fundamental and essential questions about drug abuse, ranging from the molecule to managed care, and from DNA to community outreach research. Within this science, there is a major NIDA effort to investigate issues specific to women and to study sex/gender differences. Leadership for this effort is provided by NIDA's Women & Gender Research Coordinator and Deputy Coordinator along with NIDA's Women & Gender Research Group, which has representation from all of NIDA's program branches, offices, and centers. The major goal of this effort is to infuse the study of sex/gender differences and issues specific to females in all areas of drug abuse research and to disseminate research findings in this area.

Over the past decade, the NIDA has engaged in a variety of initiatives to promote research on women and sex/gender differences and the drug abuse research field has responded as evidenced by a growing number of NIDA-supported research grants and publications in this area. Today, the NIDA supports sex/gender-based research in all of its major program areas. From basic research on the biological underpinnings and consequences of drug abuse to field research on etiology and consequences of drug abuse, to research on prevention and treatment, evidence for the importance and fruitfulness of taking a sex/gender-based research approach and analyzing data separately for males and females is growing. NIDA-supported research is repeatedly showing that sex/gender matters in drug abuse.

The research findings summarized below and published over the past 2 years are representative of the NIDA's research on women and gender differences. These research findings fall into six major research areas: 1) Biological Mechanisms and Consequences, 2) Prenatal Exposure to Drugs, 3) Nicotine Addiction, 4) Adolescents, 5) Treatment and Treatment Services, and 6) HIV/AIDS. These findings strongly suggest that the identification and understanding of sex/gender differences can improve our understanding of the nature, etiology, and consequences of drug abuse and that it may have implications for tailoring prevention and treatment interventions to maximize outcomes for both males and females.

Accomplishments

Biological Mechanisms and Consequences

NIDA-supported research over the past several years has shown that the biological underpinnings and consequences of drug abuse are not always identical for males and females. Animal studies, for example, have reported that for several drugs of abuse, females typically learn to self-administer drugs sooner and take in larger amounts than males; also, a larger percentage of females than males acquire self-administration and they exhibit stronger motivation to self-administer and exhibit a greater tendency to "relapse" following drug cessation. Sex differences have been reported in both animal and human pharmacokinetic studies as well as in studies of biological and behavioral adverse effects of abused drugs. And, both animal and human studies have clearly shown that the estrous/menstrual cycle is a determinant of drug action, both pharmacokinetic and behavioral. NIDA-supported published research over the last 2 years has built upon this growing body of knowledge. Highlighted below is animal model research on sex differences in responsivity to cocaine and opiate-induced analgesia, animal model research on adolescent nicotine self-administration, and human research showing sex differences in the impact of drugs on the brain.

Animal Models of Research

Animal Models of Sex Differences in Sensitivity to Cocaine

Prior NIDA-supported animal model research on sex differences has shown that females are more sensitive than males to cocaine during all the phases of addiction: acquisition, maintenance, dependence, and relapse. Females, for example, acquire cocaine self-administration faster and at lower doses than males, and they also self-administer more cocaine than males. In some of these studies, sex hormones have been shown to affect cocaine sensitivity in females, but not in males.

Researchers at the University of Michigan recently reported that sex hormones play a role in cocaine self-administration in females, but not males. They found that ovariectomized (OVX) females acquired cocaine self-administration slower than OVX females receiving estrogen replacement; however, castrated and non-castrated males did not differ in rate of acquisition. Both groups of females acquired cocaine self-administration faster than males, indicating that factors other than circulating estrogen account for the sex differences in acquisition of cocaine self-administration. Researchers at Hunter College of New York found that OVX females developed weaker cocaine conditioned place preference (i.e., preference for the side of the experimental chamber previously associated with cocaine) than non-OVX females, thus providing further evidence for the role of estrogen in the reinforcing properties of cocaine. Castration in males did not affect conditioned place preference. Taken together, these two studies indicate that circulating gonadal hormones play a role in the reinforcing effects of cocaine in females, but not in males, and that factors other than circulating gonadal hormones account for sex differences in the reinforcing properties of cocaine. Sex hormones also play a role in other cocaine effects. Researchers at the University of Texas found that OVX rats developed weaker cocaine-induced locomotor sensitization (i.e., an increase in the locomotor response to cocaine after repeated exposures) than OVX females with estrogen implants, thus demonstrating that estrogen plays a role in cocaine locomotor sensitization in females.

Yale University researchers have developed a rodent model that mimics human cocaine binge episodes and permits assessment of the motivation to use cocaine. In this model, for 24 hours a day rats had access to cocaine in discrete trials (four 10-min trials per hour) for 7 days. Under this binge procedure, compared to males, females self-administered more cocaine, self-administered for longer periods of time, showed greater disruption in the diurnal control over cocaine intake, and they exhibited more cocaine toxicity as evidenced by rapid weight loss and death. In order to study the effects of the 7-day binge on subsequent motivation to use cocaine, following 10 days of abstinence, the rats responded for cocaine under a progressive ratio (PR) schedule in which the number of bar presses required to obtain cocaine was progressively increased until responding eventually ceased. Females exhibited an increase in PR responding compared to their own baseline of PR responding prior to the binge period, whereas males did not exhibit this increase. These results suggest tht females may have a greater biological vulnerability to become addicted to cocaine, and once addicted, may be more motivated than males to continue to use drugs.

Researchers at Hunter College in New York have shown that sex differences in the behavioral responses to cocaine may also be mediated by sex differences in cocaine pharmacokinetics, as well as the level of the neurotransmitters dopamine and serotonin in the caudate putamen and nucleus accumbens areas of the brain. Up to 60 minutes after cocaine injection, females had higher levels of norcocaine than males. Norcocaine is a cocaine metabolite with potent effects on behavioral activity. Females also had higher serotonin basal levels than males. Serotonin has been suggested to contribute to a more robust release of dopamine, one of the major neurotransmitters involved in cocaine reward. This research indicates that sex differences in cocaine use may be related not only to differences in circulating sex hormones but also to differences in the central nervous system.

Animal Models of Sex Differences in Opiate-induced Analgesia

Animal research has shown that males are generally more sensitive to the acute effects of opiate painkillers than females. This sex difference in the antinociceptive properties of opiates has been demonstrated in mice, rats, and monkeys. Recently, research attention has focused on sex hormones, as well as the type of opiate and type of pain, as factors that may contribute to and modulate this sex difference.

Researchers at the University of North Carolina manipulated sex hormones via gonadectomy in male and female rats, and tested the analgesic effects of several opiates with varying potencies in a tail-withdrawal procedure with warm water. Consistent with prior research, greater opioid antinociception was found in intact males than in intact females with the largest sex differences occurring with the least potent opioids. Gonadectomy resulted in a decrease in opioid antinociception in males, but an increase in females, thus demonstrating that the receptor-mediated activational effects of circulating sex hormones play a role in sex differences in opioid antinociception in intact rats.

Researchers at Washington University School of Medicine have further shown that during brain development, the organizational effects of sex steroids on brain morphology and neurobiology also play a role in sex differences in opioid antinociception. They found that when male rats were castrated and female rats were masculinized with a large dose of testosterone on days 1 or 2 of life during which brain sexual differentiation is occurring, the rats responded to morphine in a manner similar to that of the untreated opposite sex. These data indicate than sex differences in morphine-induced analgesia are related to the organizational effects of sex steroids in the early development of the male and female rat brain.

Not only is the sex of the animal a critical determinant of the effectiveness of painkillers, the type of pain itself is an important factor. Researchers at the University of North Carolina, using a procedure that models post-surgical pain in humans, found that female rats were more sensitive than male rats to the painkiller buprenorphine, but there were no sex differences in the antinociceptive effects of morphine. Taken together, these recent findings indicate that both the occurrence and the magnitude of sex differences in the antinociceptive properties of opiates depend on the subject's sex, the pain assay used, and on the type of opioid tested.

Animal Models of Nicotine Effects in Adolescents

It is well documented that most adults addicted to cigarettes began smoking during adolescence. After only occasional cigarette use in adolescence, signs of nicotine dependence may occur as early as 3 weeks in females and 6 months in males. In female rats, researchers at Duke University (Dr. Levin) examined nicotine self-administration in adolescence versus adulthood as well as the persisting effects of nicotine self-administration from adolescence into adulthood. They found that adolescent females self-administered 28 percent more nicotine than adult females. Moreover, when the females began self-administering during adolescence and then continued into adulthood, they self-administered more nicotine than females that began self-administering as adults. These researchers are now studying whether this outcome occurs in males.

Adolescence-onset of cigarette smoking is of concern not only because of the health effects of smoking, but also because nicotine may alter the effects of other drugs, such as cocaine. A study of the effect of chronic nicotine on cocaine-induced locomotor activity by University of Miami researchers revealed interesting sex differences. After exposure to chronic nicotine, adolescent males were more sensitive than adult males to the locomotor effects of cocaine, whereas for females neither adolescent nor adult nicotine exposure had an effect on the locomotor effects of cocaine.

Human Research: Sex Differences in Brain Imaging Studies

The application of brain imaging techniques to drug abuse research has resulted in new insights into the effects of drugs on the brain and has yielded results that often differ in men and women. A study of cerebral blood flow in cocaine-dependent and healthy control individuals conducted at Yale University found that male cocaine users had decreased perfusion in

the anterior cingulate, right precentral gyrus, and right superior/medial frontal gyri, whereas female cocaine users had no areas of decreased perfusion, but instead exhibited increased perfusion in the posterior cingulate. These sex differences in brain perfusion among cocaine-users, along with prior research on the functions these brain regions subserve, suggest that males may be particularly at risk for relapse due to decreased blood flow in regions associated with decision-making, inhibitory control, withdrawal, and craving; whereas females may be at particular risk for relapse in response to stress. These findings suggest that different pharmacological and cognitive behavioral therapies specifically adapted for men and women may increase treatment efficacy.

Researchers at the University of Texas investigated the effect of procaine, a limbic system stimulant, on cerebral blood in cocaine-dependent individuals. Compared to healthy controls, both male and female cocaine users exhibited a blunted response to procaine in various limbic system regions, although there were sex differences in the pattern of activation. Additionally, while cocaine-dependent males exhibited increased activation in the orbitofrontal cortex, females did not. These outcomes, combined with the differences in the pharmacological properties of cocaine and procaine, suggest that chronic cocaine use may induce changes in specific receptors of the brain and that these alterations in the receptor system could offer a new framework for pharmacological interventions that perhaps are gender-tailored.

Sex differences in patterns of brain activation have also been observed in response to cocaine cues in cocaine-dependent individuals. Researchers at Emory University found that in women, cocaine cues decreased activity in the amygdala, a brain region involved in emotions, but increased amygdala activity in men. In other brain regions, cue-induced craving increased brain activity in both men and women, but in some regions the increase was greater in men than in women (ventral anterior cingulate cortex), whereas in other brain regions the increase in activity was greater in women (dorsal anterior cingulate cortex and frontal cortex). This differential pattern of activation of brain regions by cocaine cues in men and women suggests that they may use and crave cocaine for different reasons. It also suggests that they may relapse for different reasons, thus indicating that men and women may benefit from gender-specific relapse prevention strategies.

Prenatal Exposure to Drugs

It is well established that illicit and licit substances can cross the placenta and impact negatively on the fetus. Despite this fact, the 2002 National Survey on Drug Use and Health reported that 3.3 percent of pregnant women are still using illicit drugs during pregnancy, and the latest data from the Centers for Disease Control and Prevention (2002) indicate that 11.4 percent of women giving birth smoked during pregnancy. In the last decade, there has been an important decrease in smoking during pregnancy in response to public education and health campaigns; nevertheless, pregnant women are still abusing legal and illegal drugs. Highlighted below are recently published research findings from NIDA-supported research on prenatal exposure to nicotine, cocaine, and marijuana, as well as research on the effects of prenatal lead exposure on sensitivity to drug abuse in adulthood.

Prenatal Exposure to Nicotine

The risks of smoking during pregnancy for the fetus are well established and include premature delivery, low birth weight, increased neonatal mortality, and sudden infant death syndrome. Although there are unambiguous risks of smoking during pregnancy, quitting smoking is often difficult for pregnant women. Data reported by University of Chicago researchers indicated that in a sample of 1,426 pregnant smokers, mostly non-hispanic white and married, 20 percent of the women quit smoking upon learning they were pregnant, while 16 percent quit and relapsed multiple times, although often times when they resumed smoking they reduced their cigarette use.

Efforts to develop a nicotine vaccine have shown encouraging results for possible use in pregnancy. Researchers from the Minneapolis Medical Research tested an experimental nicotine vaccine during gestation in rats and found a 50 percent reduction in nicotine in the fetal brain. These preliminary data suggest that a nicotine vaccine could possibly mitigate the

effects of prenatal nicotine exposure on the fetal brain.

In addition to the risks of smoking during pregnancy described above, researchers at the University of Tennessee have recently shown that rats exposed prenatally to nicotine have an altered dopamine system, the neurotransmitter system prominently involved in drug addiction. Specifically, in rats, nicotine exposure during gestation reduces the dopamine response to nicotine in the nucleus accumbens of the brain of adolescent male and female offspring. The researchers suggest that this attenuated dopamine response to nicotine could result in enhanced susceptibility to nicotine addiction given that higher doses of nicotine could be needed in order to obtain adequate dopamine-dependent reinforcement.

Epidemiological studies have shown that the risk of SIDS triples with maternal smoking. The mechanism by which smoking contributes to this syndrome is still under investigation. It has been suggested that lack of oxygen can contribute to SIDS. Researchers at the University of Connecticut, following previous animal research, tested the hypothesis that babies of smokers have a faulty response mechanism under hypoxic conditions such as may occur, for example, when the baby is sleeping on his/her stomach. This faulty response to lack of oxygen involves the catecholaminergic system (epinephrine and norepinephrine) and rodent studies have shown that prenatal nicotine-exposure reduces the catecholaminergic response to hypoxemia in rat pups. The researchers found that at birth, babies of smokers had lower levels of epinephrine and norepinephrine than babies of non-smokers. These findings, along with those of rodent studies, suggest that maternal smoking may affect fetal catecholamine release during hypoxic stress and consequently the offspring is unable to react adequately to low levels of oxygen.

In addition to the relationship between nicotine and SIDS, there is further evidence that *in utero* nicotine exposure interferes with the development of the nervous system of the fetus. Researchers at Brown Medical School investigated the effects of smoking during pregnancy on neurobehavioral outcome of 56 newborns. They found that nicotine-exposed infants were more excitable, rigid, required more handling, and exhibited more stress/abstinence signs. Moreover, these effects were observed although the average number of cigarettes smoked per day was 6.7 in contrast to past studies in which a minimum of ten cigarettes a day were necessary to detect any deleterious effects in the newborns. As expected, the impact of smoking worsened as the mothers' smoking levels rose.

Recent data from the longitudinal Ottawa Prenatal Prospective Study, initiated in 1978 by researchers at Carleton University, indicate that the cognitive consequences of smoking cigarettes during pregnancy persist into adolescence. Assessments of children whose mothers smoked during pregnancy, conducted when the children were ages 5 to 6 and ages 9 to 12, revealed a negative association between amount of maternal prenatal smoking and overall general intelligence. At both assessments, memory deficits were exhibited. These researchers now report that at ages 13 to 16, prenatal exposure to cigarette smoking still has a negative impact on general IQ and on auditory memory with children of heavy smokers (more than a pack per day) exhibiting more deficits than the children of light smokers. Children of non-smokers in this study had an average IQ score of 113.4 while children of light smokers had an average score of 109.8 and children of heavy smokers had an average score of 105.2. Given that the distribution of IQs in the general population is normally distributed, these few differences in IQ points between the children of smokers and non-smokers could have implications for children with an IQ on the lower end of the distribution. Importantly, this shift in the IQ distribution for children of smokers could affect the number of children who require special educational services. Thus, the findings from this longitudinal study further point to the importance of developing prevention and treatment interventions for females, and especially the need for nicotine treatments for pregnant women.

Prenatal Exposure to Cocaine

Prenatal exposure to cocaine has been associated with premature birth and lower birth weight. Researchers at the Children's Hospital of Michigan recently reported that, by age 6, boys but not girls who were persistently exposed to cocaine prenatally exhibited more

cognitive and behavioral problems than boys with no or some prenatal cocaine exposure. They exhibited deficits in the areas of central processing, abstractions, passivity to the environment, and motor skills. Additionally, boys, but not girls, who received some or persistent prenatal cocaine exposure, compared to those with no exposure, were more likely to exhibit hyperactivity. These results were present even after controlling for other prenatal drug exposures, socioeconomic status, and drug use in the postnatal home environment.

Researchers at the University of Miami studied language functioning in a cohort of 200 cocaine-exposed and 176 noncocaine-exposed African American children at ages 3, 5, and 7. They found that greater language deficits were associated with greater severity of cocaine exposure. These results were independent of a variety of potential confounders including the child's level of intellectual functioning and language stimulation in the home environment.

Other research suggests that developmental outcomes associated with prenatal drug abuse can be ameliorated by the quality of the child's home environment. Researchers from the University of Maryland examined the effects of a home intervention on developmental outcomes of infants who had been prenatally exposed to a variety of substances including cigarettes, alcohol, marijuana, cocaine, or heroin. Mothers in the intervention group received weekly home visits during the first 6 months and biweekly home visits from 6- to 18-months postpartum. The infant component of the home intervention consisted of administering a comprehensive curriculum of 650 age-specific developmental skills to promote infant development. The maternal component of the intervention consisted of instructing the mothers on how to meet a variety of their self-identified needs, such as housing, public assistance programs, partner abuse, and drug treatment, by using existing services and family and social supports. Scores on the Bayley Scales of Infant Development, which was given at 6, 12, and 18 months, revealed that the home intervention had a positive effect on scores of the Bayley Mental Development Index, as well as the Bayley Psychomotor Development Index (MDI). The effects of the intervention on the MDI scores were lower if the mother reported ongoing use of cocaine and/or heroin.

The Maternal Lifestyle Study (MLS) is a large, multisite longitudinal investigation of the effects of prenatal exposure to cocaine and opiates. Researchers from the University of Miami and other participating universities have recently reported results from over 1,200 black, white, and Hispanic children, aged 1 to 3 years. Although they found marked deficits in the mental and psychomotor performances of infants with prenatal drug exposure, the deficits were not related to *in utero* drug exposure, but rather to lifestyle variables associated with heavy drug use. It is notable that women in this study had much higher rates of prenatal care than have previously been reported in studies of the effects of drug use in pregnancy, thus perhaps ameliorating possible adverse effects of cocaine. Continued developmental followup of these children is important in order to assess for possible deficits that may emerge as the children become of school age and new and advanced cognitive and psychomotor abilities develop.

Prenatal Exposure to Marijuana

Marijuana is the most common illicit drug used by pregnant women in the United States. The 2002 National Survey on Drug Use and Health indicated that 2.9 percent of pregnant women used marijuana during pregnancy. Researchers at the Carleton University, using data from the Ottawa Prenatal Prospective Study initiated in 1978, examined cognitive functioning of 13- to 16-year-old adolescents, primarily from a middle-class white population, who had been prenatally exposed to marijuana. Earlier assessments of the children had revealed deficits in memory at age 4, attention deficits at age 6, and deficits in visual integration and attention- and visual-related aspects of executive function in 9 to 12 year olds. These researchers now report that cognitive deficits persist into adolescence. Specifically, they found that prenatal marijuana exposure was related to deficits on the Peabody Spelling task and the Abstract Design test. These tests involve attention, cognitive manipulation, visual memory, analysis, and integration.

In a follow-up assessment of participants in the Ottawa study, Carleton University

researchers investigated the effects of prenatal marijuana on impulsive behavior in young adults aged 18 to 22 years. Prior research from other investigators, including these, has shown a relationship between maternal use of marijuana in pregnancy and impulsivity in children up to age 10. In the present study, the effects of prenatal marijuana on performance in the Go/No-Go task, a response-inhibition task that measures impulsivity, was assessed while functional magnetic resonance imaging (fMRI) of the prefrontal cortex of the brain was conducted. The fMRI procedure tracks changes in neural activity as measured by changes in blood oxygen levels. The prefrontal cortex of both the fetus and adult contains a high density of cannabinoids receptors and is involved in impulsive behavior. The researchers found that although all participants in the study were able to perform the task with accuracy (above 85 percent), those with prenatal marijuana exposure committed more mistakes than those without marijuana prenatal exposure. Findings from the fMRI analysis indicated that with increased prenatal exposure, neural activity increased in the prefrontal cortex and the right premotor cortex during the response inhibition task. This is the first study to report a relationship between prenatal marijuana exposure and changes in neural activity in the brain.

Prenatal Exposure to Lead

Lead present in paints, water, and soil is a public health threat to adults, children, and the fetus. During fetal development and the postnatal nursing period, lead may produce enduring developmental and neurological abnormalities. Researchers at Texas A&M University are investigating whether perinatal lead exposure in a rodent model alters sensitivity to drugs of abuse in adulthood. In an earlier study, these researchers found that the normally occurring increase in locomotor activity produced by successive administrations of cocaine was enhanced in rats exposed to lead prenatally or during lactation. These researchers have now shown that rats exposed to perinatal lead exhibit enhanced self-administration of a low dose of intravenous cocaine when tested in adulthood. Additionally, they found that in a procedure developed to model relapse in humans, rats perinatally exposed to lead exhibited enhanced relapse to cocaine self-administration. The results occurred even though in adulthood there were no differences in the level of lead in the blood or the brain between the perinatally exposed rats and those that were not exposed. These preliminary studies indicating that perinatal lead exposure may heighten sensitivity to cocaine's locomotor stimulating effects and its reinforcing effects, and may facilitate relapse to cocaine self-administration suggest the need for additional study of the linkages between environmental lead and drug abuse. In view of human data indicating that lead exposure during pregnancy and lactation can produce significant developmental and neurological abnormalities, the present data are particularly important, especially given that survey data in 1999 indicated that approximately 70 percent of inner-city children had unsafe blood lead levels and that the percentage was even higher for urban minority children.

Nicotine Addiction

The prevalence of smoking has decreased for both men and women over recent decades. Unfortunately, the rates have declined much more slowly for women than men. Although women smoke fewer cigarettes per day than men, nicotine dependence rates are higher among women than men. Further, women are less successful than men at quitting smoking, they have higher relapse rates after quitting and they have a poorer response to nicotine replacement therapies than men, thus pointing to the need for both gender-based research and female-specific research on nicotine addiction. Indeed, NIDA-supported research from basic laboratory studies with animals and humans to clinical studies of smoking cessation is increasingly demonstrating that gender plays a powerful role in the nature of nicotine dependence, its etiology, its effects, and how to treat it. In NIDA-supported studies published in the past 2 years, and highlighted below, laboratory studies have shown male–female differences in response to nicotine dose, nicotine cues, and in the types of stressful events that lead to relapse. Female-focused

research has addressed the role of estrogen therapy in postmenopausal women, as well as weight gain.

The reason for greater difficulty in smoking cessation success in women is not well understood; however, over the past several years there has been growing evidence for sex differences in factors that control nicotine addiction. Researchers at the University of Pittsburgh, for example, have recently shown that for women the dose of nicotine in a cigarettes is less important than for men indicating that nicotine *per se* might be less reinforcing for women than for men.

On the other hand, other work has suggested that cues associated with cigarettes may play a larger role in maintaining nicotine addiction in females than in males. Recently, for example, researchers at the University of Pennsylvania found that although the level of craving in response to smoking cues was the same for males and females, when the female data were separated by menstrual cycle phase, sex differences emerged. During the follicular phase (preovulatory), females had dramatically less cue-induced craving than either males or females in the luteal phase (premenstrual). These results demonstrate the importance of sex hormones in nicotine addiction in females, and further suggest that females seeking to quit smoking should perhaps consider choosing a quit date in the follicular phase when craving is lowest.

The role of sex hormones in smoking cessation also extends to the postmenopause wherein levels are attenuated. Researchers at the University of Minnesota investigated the role of estrogen and progesterone hormone therapy (HT) in postmenopausal women during a 2-week period of smoking abstinence. They found that women receiving HT exhibited an increase in depressive symptoms compared to women without HT. These results suggest that females using HT may expect more difficulties quitting smoking than women not using HT. These preliminary findings are of particular importance given the association between depressed mood and smoking relapse.

Sex differences in the effects of stressful life events on changes in smoking status were found by researchers at Yale University in a study of 1,512 former and current smokers. When stressed about financial events, compared to men, women were more likely to relapse to smoking or experience failure in attempting to quit. On the other hand, experiencing significant health events increased the likelihood of quitting in men, but not in women.

Another important factor that may contribute to differences in quitting rates between women and men is the greater weight gain in women after discontinuing smoking. Prior research has shown that smokers concerned about weight gain are less likely to want to quit and also that women are more likely than men to gain more weight following smoking cessation. Consistent with those findings, researchers at the University of Illinois have recently shown that during nicotine abstinence in women, the appeal of carbohydrate snacks is greater than in nonsmokers. This research points to the importance of addressing women's weight gain concerns in smoking cessation programs.

Research has shown that the majority of women who quit smoking during pregnancy will resume smoking during the postpartum period. Changes in mood and increases in concerns about body weight are common during the postpartum period; thus, these factors may affect women's postpartum smoking behavior. Investigators at the University of Pittsburgh reviewed the literature on postpartum relapse prevention trials and found evidence that changes in mood and weight concerns are both related to postpartum relapse. This finding suggests that smoking cessation programs that address mood changes and weight concerns could help prevent relapse in postpartum women.

Research is currently underway to promote smoking cessation during pregnancy and the postpartum. Researchers at the University of Vermont have conducted a pilot study examining the use of vouchers redeemable for retail items as incentives for smoking cessation during pregnancy and the postpartum. Women receiving vouchers that were contingent upon biochemically verified smoking abstinence had significantly better outcomes than women receiving vouchers that required no proof of abstinence. The effect remained significant at the 24-week postpartum assessment, which

was conducted 12 weeks after discontinuation of the voucher program. The magnitude of the treatment effects exceeded levels typically observed with pregnant and recently postpartum smokers.

Adolescents

Early adolescence is a time when many children begin experimentation with addictive substances, and indeed many become addicted. The study of adolescents is found in virtually all areas of NIDA-supported research and is often approached from a gender-based perspective. Findings from NIDA-supported research from the past 2 years, highlighted below, describes findings on gender differences in the prevalence of drug use, differences in risk factors for drug abuse, and differences in comoridity and treatment issues. These findings join a growing body of drug abuse research indicating that the trajectories to drug abuse and treatment issues are not identical in boys and girls and that taking a gender-based approach to prevention and treatment interventions can perhaps lead to better outcomes in boys and girls.

Gender Differences in the Prevalence of Drug Abuse among Adolescents

Monitoring the Future, NIDA's annual prevalence study of adolescent illicit drug use, found that in 2004 slightly more 12th grade boys than girls used illicit drugs, but in the 8th and 10th grades there were minimal gender differences in use. When marijuana was excluded from the analysis of illicit drug use, however, the rate of use by 8th and 10th grade girls was 2 percent greater than for boys. Marijuana use in the 8th and 10th grades was only slightly greater in males than females, but the gap widened in the 12th grade. Of especial concern is the finding that since 1992 the use of inhalants by 8th grade girls has been greater than for boys, and for years 2002, 2003, and 2004, use by 10th grade girls also surpassed that of boys. There is also a long-term trend, starting in 1991, of greater amphetamine use by girls than boys in the 8th and 10th grades, although few gender differences are present in the 12th grade. Since 1999, 8th grade girls have also surpassed boys in methamphetamine use, but by the 10th grade there are few gender differences.

Researchers at the University of Michigan examined ethnic differences in licit and illicit drug use among 8th-, 10th-, and 12th-grade students with a particular focus on girls. Utilizing data from the Monitoring the Future study from years 1996 to 2000 they found that among girls, both licit and illicit drug use was widespread with trend data suggesting that girls' and boys' drug use patterns are converging. Among adolescent girls, data on ethnic differences indicated that marijuana use on average was highest among Native American girls, somewhat lower among Mexican American, Puerto Rican, and white girls; lower still among African American and other Latinas; and lowest among Asian American girls. Native American girls across all three grades were also highest on use of other illicit drugs, generally followed by Mexican American and white girls, Puerto Rican and other Latinas, and Asian American and African American girls. This research shows a reduction in the drug use gap between boys and girls and it points to the importance of identifying ethnic differences in drug use in order to develop culturally appropriate interventions.

Gender Differences in Risk Factors for Drug Abuse in Adolescents

Recent research has added to the growing body of literature showing that genetic and environmental risk factors for drug abuse are not always identical in males and females. Researchers at the University of Colorado, for example, conducted a sibling/twin/adoption study of 2,124 adolescents, aged 12 to 19 years, to investigate the influence of genetics on the initiation, use, and problem use of tobacco, alcohol, marijuana, and other illicit drugs. Consistent with findings from similar studies with adults, problem use was found to be more heritable than initiation and use. Heritability, however, was not uniformly equal in males and females. Heritability was higher in females than in males for marijuana initiation, tobacco use, and tobacco problem use; however, there was no evidence for higher heritability in males than females either in initiation, use, or problem use for any of the investigated drugs.

Previous research has shown that "difficult temperament" and deficits in cognitive functioning are associated with drug use/abuse

in youth. Researchers at the Universities of Kentucky and Pittsburgh examined the interaction of low executive functioning (the abilities of problem solving, attentional control, and goal planning) and "difficult temperament" in a sample of 340 adolescent girls with and without substance abuse disorder. They found that "difficult temperament" was a predictor of drug use, regardless of the level of executive functioning. Low executive functioning, however, was a predictor of drug use in girls with good temperament, but not in girls with difficult temperament.

Several studies have shown that children in families headed by drug-dependent parents exhibit more behavioral and emotional problems. Often in these families, there are frequent changes in the individual who serves as the primary parental caregiver for the children. Recently, researchers at the University of Chicago conducted a longitudinal study of children with at least one parent in a methadone maintenance program. This study prospectively examined, over a $2^1/_2$-year period, the relationship between the number of changes in parental role figures the children experienced and subsequent delinquency and drug abuse. The researchers found that increased parental figure transitions was related to subsequent delinquency in both boys and girls, but had opposite effects on drug use in boys and girls. Whereas in girls the probability of drug use increased dramatically with increases in the number of parent figure transitions, the probability of drug abuse decreased somewhat in boys. These findings point to intervention needs of children of parents in drug abuse treatment and especially the need for gender-sensitive interventions that address the issues associated with changes in parental figure transitions.

Another important environmental factor in the initiation and use of drugs is physical and sexual abuse during childhood and/or adolescence. Researchers at the National Development and Research Institutes in New York City investigated the relationship between a history of physical and sexual abuse and substance abuse among 470 men and women admitted for detoxification in an inpatient facility. Researchers found that an exceptionally high number of men and women had been physically or sexually abused: 81 percent of the women and 69 percent of the men. For 75 percent of these individuals, the abuse first occurred prior to age 18. A significant association with substance abuse was found for men if the abuse occurred prior to age 18. For women, the association of physical/sexual abuse with substance use was similar across all ages. These findings suggest that after age 17, males may be less vulnerable to the substance abuse risk associated with physical/sexual abuse, whereas females are vulnerable regardless of age of abuse.

Other researchers at the National Development and Research Institutes studied a special form of sexual abuse found in inner-city girls living in distressed, impoverished, unstable households characterized by high levels of drug abuse. This ethnographic study of 72 inner-city New York households, predominantly self-identified as Black or African American, investigated the phenomenon they termed "compelled childhood sexual contact." They found that this compelled sex began in early childhood and continued through adolescents and into early adulthood. Within the family context of these households, compelled sex is viewed as normative. At times it is even encouraged, or the victim's complaint is minimized, or she is accused of lying. Results of this study suggest that compelled sex becomes integrated into the social–developmental process by which these young women learn that sexual favors can be exchanged to meet a variety of needs such as food, clothing and shelter, intimacy, and avoidance of physical assault. In particular, the girls learn that sex can be exchanged for drugs. Research is needed that will allow early identification of the victims, and interventions must be developed that focus on interrupting the cycle of parental drug use, serial sexual abuse, and the exchange of sex for drugs.

Gender Differences in Comorbidity and Treatment Issues among Adolescents

Comorbidity of substance abuse disorders (SUD) and psychiatric disorders often occurs at high rates among adolescent substance abusers, especially those with a history of sexual or physical abuse. Adolescents with comorbid disorders have earlier onset of

substance use, greater frequency of use, and more chronic use. In order to meet the challenge of treating this population, the relationship between the comorbidity and treatment outcome must be clearly understood, and treatment interventions targeting substance abuse, psychiatric disorder, and abuse must be developed.

Researchers at the University of Miami investigated the relationship between comorbidity and drug abuse treatment response among 182 adolescent drug abusers, aged 12 to 17. They found that the most severe comorbidity occurred in females, in individuals with greater family dysfunction, and in individuals who were younger at treatment entry. Independent of gender, there was a strong link between comorbidity and poor treatment response. Further, a University of Arizona treatment study compared adolescent males and females, and low versus acute levels of traumatic stress. Findings indicated that compared to males and those with low levels of traumatic stress, females and those with acute levels of traumatic stress symptoms had higher degrees of substance use and mental health and physical health problems, as well as greater HIV sex-risk behavior.

Researchers at Duke University conducted a longitudinal study with 1,420 boys and girls aged 9 to 13 at intake in which they assessed for DSM-IV disorders, including SUD, annually until age 16. An examination of the relationship between SUD and other psychiatric disorders revealed that girls, but not boys, with anxiety disorder or conduct disorder were at increased risk for SUD. The other DSM disorders that were assessed, including depressive disorder, behavior disorder, oppositional defiant disorder, and ADHD, were not found to be related to later development of SUD. The increased risk of SUD in girls with anxiety disorder and conduct disorder point to the need for early interventions targeted at girls with these disorders.

UCLA researchers examined the effects of physical and sexual abuse on treatment processes and posttreatment abstinence among 803 adolescents in 23 treatment facilities in four major U.S. cities (Pittsburgh, Minneapolis, Chicago, and Portland). Findings indicated that 59 percent of the females and 39 percent of the males reported a history of sexual and/or physical abuse. Boys reported higher rates of physical abuse alone (34.1 vs. 17.5 percent), while girls reported higher rates of sexual abuse alone (15.8 vs. 0.9 percent) and both physical and sexual abuse (25.4 vs. 4.3 percent). Abused adolescents, compared to the non-abused, had more severe substance use and higher rates of conduct disorder, ADHD, and depression. The rate of depression in non-abused youth was equivalent in males (8.2 percent) and females (9.1 percent), but among abused youth the rate of depression in girls (30.5 percent) was twice that of boys (15.8 percent). In general, abused adolescents reported a greater number of family, health, and mental health services needs than non-abused adolescents. The highest number of perceived needs among the four groups was reported by abused girls. The highest rate of participation in 12-step groups was among non-abused girls and the lowest was among abused girls. On measures of counselor rapport, boys scored higher than girls, and abused girls scored higher than non-abused girls. Furthermore, abused girls scored higher than all three groups on measures of perceived treatment effectiveness. Rates of treatment retention and posttreatment abstinence were equivalent in abused and non-abused youth, but were greater for girls than for boys. The likelihood of posttreatment abstinence was lower for youth with a history of physical abuse (with or without sexual abuse), except for those who had better rapport with their counselors. These findings suggest that treatment outcome for abused girls can be greatly improved if counselor–client rapport becomes a focus of treatment rather than 12-step groups.

Treatment and Treatment Services

Over the past several years, NIDA-supported treatment and services research has increasingly focused on special issues related to women. This research has also increasingly adopted a gender-based approach, as this approach is increasingly yielding important information on both males and females. This gender-based approach, for example, is revealing widespread gender differences, including treatment entry characteristics, treatment and services needs, barriers to treatment, treatment engagement and retention, treatment outcomes, and relapse predictors. Such research shows, for example,

that women may be less likely to enter treatment than men, have shorter lengths of stay, and lower rates of treatment completion. Ongoing NIDA-supported treatment and services research includes targeted groups of women, including women who are mothers, women who are pregnant or postpartum, women offenders, homeless women, women with drug-using partners, minority women, and women experiencing current and past violence and trauma. Continuing research into the specific needs of women who need treatment, including these subgroups of women, is necessary in order to increase success at getting women to begin treatment, and once there, to complete treatment and have successful long-term outcomes. NIDA-supported published research over the last 2 years, highlighted below, includes targeted research on women, including those with the dual diagnosis of posttraumatic stress disorder (PTSD) and substance use disorder (SUD), those who are in residential treatment with their children, and those who have a drug-abusing partner. Other research highlighted below reveals important gender differences in treatment outcomes in research on treatment of cocaine and opiate dependence.

Comorbidity of Posttraumatic Stress Disorder and Drug Dependence

The comorbidity of PTSD and SUD is of particular importance in the treatment of substance abuse in women. Women with this dual diagnosis display a more severe clinical profile, have multiple complex needs, and a poorer treatment prognosis than women without this dual diagnosis. Researchers at the Affiliated Systems Corporation in Texas assessed the comorbidity of cocaine abuse with physiological dependence (CD) and PTSD in a sample of 347 African American and Hispanic cocaine users. They found that 29 percent met the criteria for dual diagnosis of PTSD/CD, but that race/ethnicity was not a significant factor in this dual diagnosis. Being a women, however, increased the likelihood of the PTSD/CD dual diagnosis, and being a young female increased it even more.

Researchers at the University of South Carolina examined differences in substance abuse severity, trauma history, PTSD symptomatology, and psychiatric comorbidity among 74 treatment-seeking women with PTSD along with either cocaine dependence (CD) or alcohol dependence (AD). They found that the profiles of PTSD/CD women were different from those of the PTSD/AD women. PTSD/CD women exhibited greater occupational and social impairment and reported more legal problems, including high rates of prostitution, whereas PTSD/AD women reported greater exposure to non-crime traumas, higher rates of major depression and social phobia, and received higher scores on avoidance, hyperarousal, and intrusion. These findings suggest that substance-abusing women with PTSD are not a homogeneous group and, therefore, treatment interventions are needed that more clearly reflect these differential dual-diagnosis profiles.

Two manualized cognitive behavioral therapies have recently shown promise in the treatment of women with concurrent SUD and PTSD: Seeking Safety, which addresses both PTSD and substance abuse, and Relapse Prevention, which addresses only substance abuse. Researchers at the St. Luke's Roosevelt Hospital Center compared the efficacy of these two manualized cognitive behavioral therapies with that of standard community care in a group of low-income women with SUD/PTSD. Three months posttreatment, participants in both cognitive behavioral groups had significantly reduced substance use, PTSD, and psychiatric symptoms, whereas the community-care participants had worsened. At 6- and 9-month follow-ups, the two cognitive behavior therapy groups equally sustained superior improvement in all areas compared to individuals in the community-care group. These outcomes suggest that Seeking Safety and Relapse Prevention are efficacious short-term treatments for low-income urban women with PTSD, substance use disorder, and other psychiatric symptoms. These findings have been corroborated by preliminary findings in a Brown University study in which Seeking Safety was used in the treatment of incarcerated women with SUD/PTSD. Data indicated that at the end of treatment, 53 percent of the women no longer met criteria for PTSD; 3-months posttreatment, 46 percent of the women still no longer met criteria for PTSD. Importantly, at 6-weeks posttreatment 79 percent of the women

had abstained from substance use, and at 3-months posttreatment 65 percent continued to remain abstinent.

In a Brown University treatment utilization study of women with PTSD/SUD, researchers conducted a survey of women's preferred focus of treatment. Findings from the survey, completed at treatment entry, indicated that 80 percent of participants preferred either a combined focus on substance abuse and PTSD or a focus on PTSD alone, while a smaller percentage preferred a focus on substance abuse only (18.4 percent) or neither focus (1.3 percent).

Residential Treatment for Women and Their Children

A major issue for drug-abusing women is the loss of co-residency with their children. This loss may be associated with drug abuse itself or it may be associated with entry into drug treatment. Researchers at UCLA and Columbia University studied the living arrangements of children whose mothers were undergoing detoxification and found that only 21 percent of the 256 mothers were the guardians of all of their minor children. Researchers at the Texas Christian University examined the effect of maintaining or reuniting children and mother at treatment entry on their subsequent co-residency after treatment. The sample consisted of 152 mothers, 35 percent of whom had custody of their children and brought all with them to treatment, and 65 percent who were living apart from at least one child at admission. Families lived in independent apartments and children attended on-site child care or school and were integrated into the treatment program. Mothers received drug abuse treatment as well as support in maintaining responsibility for family management (e.g., food, clothing, and nurturance). At 1-year follow-up, findings indicated that mothers who resided with all of their children prior to treatment entry and during treatment, as well as mothers who were reunited with their children at admission, were over five times more likely to co-reside with their children than mothers who were separated from their children prior to treatment, including those reunited after the treatment process began. These findings suggest that co-residency of mother/children at admission to treatment is beneficial in maintaining long-term co-residency.

Residential care that includes children need not be costlier than other types of residential programs. Safehaven, a comprehensive 50-week residential treatment program located in Key West, Florida, within a public housing complex, was subjected to a cost/benefit analysis by University of Miami researchers. The program provides therapeutic interventions for women and children, focuses on the development of self-sufficiency skills, and encourages gainful employment. Findings indicated that weekly costs for Safehaven were only slightly higher than for other drug treatment residential programs, while treatment retention rates were considerably higher (62 vs. 43 percent). These findings are of particular significance because length of stay is an important benchmark for treatment success. The average length of stay at Safehaven is 322 days versus 171 days for other residential drug treatment programs.

Women with Drug-abusing Partners

Treatment retention and relapse are especially important issues for women with drug-using partners. UCLA researchers, utilizing data from the Chicago Target Cities Study and the Persistent Effects of Treatment Study, examined gender differences in relapse among 903 individuals receiving treatment in a variety of treatment modalities. At the follow-up, conducted 6-months after the end of treatment, the researchers found that for women, but not men, living with a drug-abusing partner was predictive of relapse. Researchers at the Johns Hopkins University School of Medicine surveyed pregnant women enrolled in their comprehensive treatment program and found that 49 percent of the women had a male drug-abusing partner. Those drug-using partners had more unemployment, more current legal involvement, and less education than drug-free partners. They were more likely to provide their pregnant partner with money for drugs, and were less likely to be supportive of their recovery. Women with a drug-abusing partner were retained in treatment for an average of 52 days while those with drug-free partners were retained for 73 days. This data strongly suggest that in

order to ensure a more positive treatment outcome for women with drug-abusing partners, treatment research is needed that targets those partners.

Gender Differences in Treatments for Cocaine and Opiate Dependence

Some important gender differences have recently been found in the treatment of both cocaine and opiates. The medication, disulfiram, approved for the treatment of alcoholism, has recently been shown effective for the treatment of cocaine dependence as well. Researchers at Yale University tested for gender differences in the effectiveness of disulfiram in treating cocaine dependence, and found that it was limited to men. Men treated with disulfiram had a higher percentage of cocaine-free urine specimens than those taking placebo, whereas in women there were no differences in outcome between those taking disulfiram versus placebo. These findings highlight the importance of routine gender analysis in the testing of new medications for the treatment of drug abuse.

Many methadone-maintained individuals continue illicit drug use despite receiving the combined treatments of methadone, drug counseling, and contingency management. Researchers at the Massachusetts General Hospital piloted a cognitive–behavioral treatment therapy for interoceptive cues (CBT-IT) which was developed specifically for the reduction of illicit drug use among methadone-maintained individuals. CBT-IT involves the induction of interoceptive cues (emotional and somatic) associated with drug craving and the training of self-control techniques (e.g., cognitive coping procedures, over-rehearsed behavioral responses, and relaxation and diaphragmatic breathing) to help patients tolerate and respond to those cues. Participants were outpatients who, despite 3 months or more of regular attendance at a methadone program providing weekly counseling, had failed to control their illicit drug use. Patients were randomly assigned to either the experimental CBT-IT program or a control program of increased weekly counseling. Findings indicated that in women CBT-IT exhibited significantly greater reductions in illicit drug use than those receiving intensified counseling, whereas in men, intensified counseling produced better outcomes than CBT-IT.

A cocaine treatment study conducted at the Providence VA Medical Center compared a cocaine-specific coping skills training (CST) program and an educational discussion (ED) program. The CST involved both analyzing the thoughts and emotions that surround episodes of cocaine use, and developing alternative cognitive and behavioral skills to reduce the risk of use. Findings indicated that at 1-year follow-up, women in the CST group were less likely to use cocaine and alcohol than women in the ED group. At the 6-month follow-up, a gender analysis revealed that within the CST group, women were less likely to relapse to cocaine than men. And, at 1-year follow-up, women within the CST group used cocaine and alcohol less frequently than did men.

HIV/AIDS

According to the 2003 CDC HIV/AIDS Surveillance Report from 1999 through 2003, the number of AIDS cases in the United States increased 15 percent among women, but only 1 percent among men, with two-thirds of women affected being African American. Injection drug use accounted for a greater percentage of HIV infection in women than in men: 38 percent of the cumulative AIDS cases in women were among injecting drug users (IDUs), whereas IDUs accounted for 21 percent of the cumulative AIDS cases in men. An additional 15 percent of AIDS cases among women, compared to 1 percent of AIDS cases among men, were associated with sex with an IDU. In all, AIDS cases among U.S. women were much more likely to be directly or indirectly (through sex with an IDU) related to injecting drug use as compared to men (53 vs. 22 percent).

Among adolescents aged 13 to 19, as among adults, the number of AIDS cases in males has historically outnumbered the cases in females, but by the end of 2002, the cases in males and females were equivalent (CDC 2002). As with adults, IDU accounted for a larger percentage of adolescent AIDS cases in females than males. Adolescent males who have sex with males represented 41 percent of the male cases, injection drug use represented 10 percent, and infection through heterosexual

contact represented 6 percent. For females, infection through heterosexual contact represented 66 percent of reported AIDS cases and IDU represented 19 percent.

These gender differences in mode of transmission of HIV clearly point to the need for gender-specific approaches in understanding risk factors and in developing prevention interventions that target the intersection of drug abuse and HIV/AIDS in women. Recently published NIDA-supported research has continued to identify gender differences in HIV risk behaviors and has identified risk factors in specific subgroups of drug-abusing women, including heroin sniffers who do not inject drugs and women who have sex with women. Among women with HIV/AIDS, African American women are disproportionately affected and recent NIDA-supported research has shown promising results from interventions that specifically target them.

Female-specific Risk Factors and Subgroups of At-risk Females

Researchers at the Johns Hopkins University used data from two longitudinal cohort studies, ALIVE and REACH mega project, with over 2,000 IDUs and non-injecting drug users (NIDU) in Baltimore, to investigate sex differences in the effects of drug use and sexual risk factors in the acquisition of HIV infection. The REACH mega project revealed that males and females shared two HIV risk factors: having injected speed balls or cocaine and being of younger age. Both studies found that among females IDUs, there were two variables associated with HIV: having a male drug-using sexual partner and having had a sexually transmitted disease. Additional REACH mega project risk factors identified for males were having sex with another male, being African American, having shared needles in the last 6 months, and having a short transition from NIDU to IDU. An additional risk factor in females was having had first sexual intercourse before the age of 15. In the ALIVE project, other risk factors for males included daily IDU, cocaine IDU, attending shooting galleries, and education lower than high school. Additionally, IDU males who engaged in homosexual activity doubled their chances of being seropositive. These results highlight the differential roles of sexual risk behaviors and IDU in the acquisition of HIV infection in male and female drug users.

Researchers at Columbia University examined HIV risk factors in a racially/ethnically diverse sample of 285 HIV-negative male and female non-injecting heroin users. They found that females were more likely than males to have drug-using partners, to use heroin with their partners, and to have partners at known risk of being HIV infected. They further found that women were more likely than men to trade sex for a reliable supply of drugs, money, or both, thus increasing their HIV risk.

Researchers at the National Development Research Institutes examined condom use among 193 young adult drug users, aged 18 to 24, who were predominantly Latino/a. The results were based on their 377 non-commercial heterosexual relationships occurring over the prior 12-month period. The researchers found that consistent use of condoms in these relationships was reported by 25 percent of the males and 29 percent of the females. They also found that when men's peers approved of condom use, they tended to use them as well. This relationship did not hold for women, perhaps because, as suggested by the researchers, these young women may have less control over condom use in their relationships than do males. Indeed, in a Columbia University study of resource acquisition strategies of low-income NYC inner-city women who use drugs, the researchers found that because of the women's economic dependence on men for various resources (e.g., drugs, money, housing, and food) which they receive in exchange for sex, their ability to negotiate condom use is often minimal or non-existent. These results point to the need for prevention efforts and interventions that train drug-using women to be empowered in their relationships and to increase their economic independence of males as a means of reducing their HIV-risky sexual behaviors.

Investigators at the University of Miami have found that risky sexual behavior plays a major role in HIV-risk women who use heroin intranasally (sniffing), but have no history of injection drug use. They found that in a sample of 241 ethnically/racially diverse heroin sniffers, the prevalence of HIV in women was over twice that for men (18.1 vs. 8.7 percent), even

though both women and men engaged in high risk sexual behaviors. Females had higher rates of crack use than males and were more likely to use crack daily (47.6 vs. 27.4 percent). Furthermore, a direct relationship between frequency of crack use and the number of sexual partners was found in women, but not in men. The higher HIV prevalence among female heroin sniffers may be a consequence of their being more likely than men to receive drugs or money in exchange for sex.

Another recently identified group of drug-using women at risk for HIV infection are women IDUs who have sex with women (WSW). In a sample of 803 black, white, and Hispanic IDU women in six sites across five cities, researchers at the National Development and Research Institutes in New York found that 274 women (34.12 percent) reported having had sex with a woman during the preceding 6 months. These women, compared with non-WSW IDUs, had higher HIV rates. They were also more likely than non-WSW IDU women to have been institutionalized or homeless, to have engaged in receptive syringe sharing, to have shared rinse water, and to have engaged in sexual intercourse with a wide variety of high HIV-risk individuals, including MSM IDUs, older IDUs, WSW IDUs, and IDUs who had HIV or hepatitis. This research points to the need for interventions that target female IDUs who have sex with women and address their specific risk factors and socioeconomic needs.

HIV/AIDS Interventions for African American Women

The African American community is disproportionably affected by the AIDS epidemic. In the United States in 2003, African Americans accounted for 42 percent of all the people living with AIDS. The rate of AIDS diagnoses for African American was almost ten times the rate for whites, and almost three times the rate for Hispanics. The rate of AIDS diagnoses for African American women was 25 times the rate for white women, whereas the rate of AIDS diagnoses for African American men was eight times the rate for white men. In 2001, HIV/AIDS was the leading cause of death in African American women, aged 25 to 34, and the third leading cause of death in the 35 to 44 age group (CDC, 2001). Thus, much NIDA-supported research has focused on identifying factors that put them at risk for HIV. Data from several recent studies from the University of North Carolina, as well as from University of Missouri, suggest that the combination of drug use, homelessness, violence, and mental health disorders, such as depression, anxiety, and posttraumatic disorder, may predispose African American women to engage in risky sexual behavior at a higher rate than other populations of women. These studies suggest that interventions for African American women should be tailored to addressing their specific needs for a variety of psychosocial services.

Promising outcomes from interventions specific to African American women have been recently reported. Researchers at RTI International in North Carolina developed and tested a gender-tailored, culture-specific adaptation of the standard NIDA HIV prevention intervention. Of the 620 female participants, 213 were in the women-focused group, 199 in the standard intervention group, and 207 in a control group that received a delayed standard treatment. The women-focused intervention included culturally enriched content grounded in empowerment theory and African American feminism. It also acknowledged the specific barriers (e.g., pervasive poverty and violence) facing African American women and how these barriers affect daily experiences and choices. All three groups significantly reduced crack use and high-risk sex behaviors in the 6-month follow-up. Of the three groups, the women in the women-focused intervention reported the greatest reduction in crack use, the lowest percentage of homelessness, and were least likely to engage in unprotected sex.

The importance of culture-focused programs was also demonstrated by researchers at Emory University who developed a culture- and gender-specific HIV intervention program for drug-addicted African American women. In this intervention, involving 333 women, the NIDA standard HIV intervention program was enhanced by addressing sociocultural issues relevant to African American women. In the 6-month follow-up, women in the enhanced intervention, compared to those in the standard intervention, had a greater decline than

women in the standard intervention in the number of drug injections, in the number of sexual partners, and in the frequency of having sex while high. They also had an increase in the frequency of condom use and in self-initiating drug treatment attendance as compared to women in the standard program. These findings emphasize the importance of culturally appropriate interventions in the prevention of HIV-risk behaviors in African American women.

Initiatives

The NIDA continues to engage in a variety of activities to promote research on women and sex/gender differences and to disseminate research findings in this area. Included in these efforts are special programs targeting the next generation of researchers, program announcements and requests for applications, clinical trials initiatives, funding collaborations with the ORWH and other NIH ICs, publications, planning events at scientific conferences, and making presentations.

Program Announcements (PAs)

- **Women, Gender Differences, and Drug Abuse**
  In 2003 NIDA issued this PA which calls for research on women and sex/gender differences in all areas of drug abuse research. (PA-03-139)

- **Targeted Integrative Research in Drug Abuse and HIV/AIDS in Pregnancy**
  NIDA issued this PA in 2004.
  (RFA DA-04-010)

During 2003 and 2004, NIDA issued or continued several other program announcements that solicit research containing an emphasis on sex/gender differences and issues specific to women:

- **Collaborative Clinical Studies in Drug Abuse**
  (PA-01-039)

- **Drug Abuse Health Services Research**
  (PA-01-097)

- **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment Services and Women and Gender Differences**
  (PA-02-055)

- **Neuroscience Research on Drug Addiction**
  (PA-02-085)

- **Services Research in the National Drug Abuse Clinical Trials Network**
  (PA-03-011)

- **Behavioral Therapies Development Program**
  (PA-03-126)

- **Molecular Genetics of Drug Addiction Vulnerability**
  (PA-03-155)

- **Drug Abuse Aspects of HIV/AIDS and Other Infections**
  (PA-04-007)

- **Epidemiology of Drug Abuse**
  (PA-04-100)

- **Prescription Drug Abuse**
  (PA-04-110)

- **Health Disparities among Minority and Underserved Women**
  The NIDA participates in this PA which was released in August 2004.
  (PA-04-153)

Clinical Trials

Through research project grants, the NIDA is making important progress in initiating women-specific clinical trials addressing a variety of topics, including smoking cessation in pregnant and non-pregnant women, domestic violence prevention, treatment of drug-abusing pregnant women, drug-abusing women with comorbid posttraumatic stress disorder, and HIV prevention. As part of this effort, the NIDA's Clinical Trials Network has initiated four multi-site protocols relating to women:

- **Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Abusers**

- **Women's Treatment for Trauma and Substance Use Disorder**

- **Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment**

- **Brief Strategic Family Therapy for Adolescent Drug Abusers**

Fostering the Next Generation of Researchers

The NIDA actively seeks to increase the number of new drug abuse investigators who conduct research on women and sex/gender differences. The following special programs contribute to that effort:

- **Women & Gender Junior Investigator Travel Awards**
  Since 2000, the NIDA has made competitive travel awards available to junior investigators who present their research on women or sex/gender differences at the annual meeting of the College on Problems of Drug Dependence. An award of $750 is provided to 30 recipients.

- **Dissertation Awards**
  In 2002, NIDA issued the program announcement, Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services and Women and Gender Differences (PA 02-055), which provides support for predoctoral students whose dissertation on drug abuse focuses on women and/or gender differences. This announcement will be re-issued in 2005.

- **Building Interdisciplinary Research Careers in Women's Health (BIRCWH)**
  Under this ORWH-led initiative that funds 12 grants awarded in 2000, research career development support is provided to junior faculty members who are commencing basic, translational, behavioral, clinical, and/or health services research relevant to women's health and sex/gender differences. The NIDA provides co-funding for the three grants that provide mentoring to junior faculty members wishing to pursue a program of drug abuse research on women's health and sex/gender differences. Those NIDA BIRCWH sites are the University of Kentucky, the Virginia Commonwealth University, and Yale University. The NIDA is also participating in the re-issuance of the RFA for this program, RFA-OD-05-002, Building Interdisciplinary Research Careers in Women's Health, released November 24, 2004. (OD-99-008)

Other NIH Collaborations

- **ORWH SCOR Program**
  Eleven 5-year centers were established under the ORWH-led initiative, Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health. The NIDA provides co-funding for the two centers that focus on drug abuse: Sex and Gender Factors in Drug Abuse, located at the Medical University of South Carolina, and Sex, Stress and Cocaine Addiction, located at Yale University. (RFA OD-02-002)

- **Maternal Lifestyle Study**
  The Maternal Lifestyle Study (MLS), a multi-site project funded by the NICHD and the NIDA since the early 1990s, is a longitudinal study investigating the health and development of children exposed to cocaine and opiates during pregnancy, and also includes study of maternal perinatal complications and pregnancy outcomes. Measures include a range of child and maternal outcomes, as well as numerous potentially confounding social and environmental factors. The largest study of its type, MLS has sites in Detroit, Memphis, Miami, and Providence. The children have been followed since birth, and the oldest are now 11 years of age.

- **Women's Interagency HIV Study (WIHS)**
  This NIAID/NIDA/NICHD/NCI/NIDCR cooperative agreement supports a very unique multidisciplinary, multi-site study of HIV/AIDS progression in a large cohort of women. Since a large percentage of women at risk for HIV/AIDS are drug abusers, this study provides information on women for whom drug abuse is a factor in their HIV/AIDS.

- **MRI Study of Normal Brain Development**
  The NIDA is a participant in this collaborative initiative with the NINDS, the NIMH, and the NICHD which will, for the first time, provide a developmental database (both longitudinal and cross

sectional) of the structural maturation of the human brain from birth to the age of 18, along with data on associated neurobehavioral and neuropsychological maturation. This project, which was initiated in 2000 and will end in FY 08, is conducted at six pediatric study centers and two coordinating centers and will eventually enroll 500 male and female children. While there are known sexual dimorphisms in the adult human brain, these have never been tracked developmentally. Thus, for the first time, this initiative will provide data that characterize the developmental emergence of these sexually dimorphic brain changes. Such data will provide the NIDA with important norms against which to assess sex differences in the effects of abused drugs on the developing brain and associated behavioral correlates.

Publications

Publications that address women, sex/gender differences and drug abuse are important means by which the NIDA can disseminate research findings and encourage further research in this field. The following NIDA publications serve these goals.

- ***Women's Health and Gender Differences: A Collection of Articles from NIDA Notes***
  A compilation of research articles from the *NIDA Notes* newsletter. This collection was originally published in 1996 and is revised periodically, most recently in 2004.

- ***Women, Gender Differences, and Drug Abuse*: *Excerpts from the Director's Report to the National Advisory Council on Drug Abuse***
  This publication is a compilation of research findings on women, sex/gender differences, and drug abuse that are reported in the quarterly Director's Report to the National Advisory Council on Drug Abuse. It is updated annually and contains research findings dating back to February 1995.

- ***Successfully Including Women in Clinical Trials: A Guide for Researchers***
  This brochure, published by NIDA's Clinical Trial Network, is designed to aid drug abuse investigators in their efforts to include women in clinical trials. Published originally in December 2002, a Spanish translation was published in April 2003. The brochure is undergoing revision and will be ready for publication later in 2005.

- ***Focus on Women & Gender Differences: Mini-Program***
  Prepared for the College on Problems of Drug Dependence (CPDD) annual conference since 2000, this mini-program book is a partial replication of the CPPD program book, but contains only those program listings related to women and sex/gender differences. Additionally, it contains the CPDD abstracts on women and sex/gender differences, as well as information on the recipients of the Women & Gender Junior Investigator Travel awards given by the NIDA, announcement of the travel award program for the following year's CPDD meeting, and information on NIDA's current program announcements that focus on women and sex/gender differences.

Website

The website, Women and Gender Research, became operational on NIDA's website in April 1998 and is regularly updated. Topics include an overview of NIDA's research program in this area, research findings, publications, and funding opportunities.

Conferences and Workshops

A major way in which the NIDA attempts to increase research on women and sex/gender differences is to spotlight this research at conferences and conventions by planning, supporting, and participating in symposia and roundtable discussions at scientific meetings. Below are examples from 2003 and 2004:

- **Recruitment and Retention of Participants in Drug Abuse Research: Incentives, Ethics, and Practical Considerations**
  Expert panel at the conference, Science Meets Reality: Recruitment and Retention of Women in Clinical Studies, and the Critical Role of Relevance, sponsored by the NIH Office of Research on Women's Health, January 6-9, 2003.

- **Addiction – Addressing the Biology and Behavior of Addiction**
  This was at the working group meeting, Women, Tobacco, & Cancer: An Agenda for the 21st Century, in Houston, Texas, February 3-5, 2003.

- **Drug Abuse as a Gender Issue**
  Symposium at the annual meeting of Experimental Biology, April 11-15, 2003, San Diego.

- **Can Prevention Studies Inform Etiological Research? A Case Study Involving Gender Effects in Prevention Research**
  Roundtable at the annual meeting of the Society for Prevention Research, in Washington, DC, June 13, 2003.

- **Substance Abuse Prevention, Treatment, and Service Delivery for Adolescent Girls**
  Symposium at the annual meeting of the American Psychological Association, in Toronto, Canada, August 7-10, 2003.

- **Smoking Cessation: The Right Treatment for the Right Gender**
  Symposium at the National Conference on Tobacco or Health, in Boston, MA, December 10-12, 2003.

- **What We Need (and Pay) to Know about Girls, Women and Gender: Research Needs and Development Opportunities at NIH and CDC**
  Symposium at the executive committee meeting of American Psychological Association Division 35, Society for the Psychology of Women, at American Psychological Association Headquarters in Washington, DC, February 5, 2004.

- **Drug Abuse Treatment Issues in Women**
  Symposium at the annual meeting of the American Psychiatric Association, in New York City, NY, May 1-6, 2004.

- **Drug Abuse Treatment Issues in Adolescent Girls**
  Symposium at the annual meeting of the American Psychological Association, in Honolulu, HI, July 28-August 1, 2004.

- **Drug Abuse and Psychopathology in Women: Blending Research and Practice**
  Roundtable discussion at the annual meeting of the American Psychological Association, in Honolulu, HI, July 28-August 1, 2004.

Invited Talks Given by NIDA Staff

In addition to sponsoring and participating in symposia and roundtable discussion, the NIDA's Women & Gender Research Coordinator and other NIDA staff also give invited talks on the scientific progress and research gaps. Below are examples from 2003 and 2004:

- Lecture: **Sex Differences in Nicotine Dependence**
  Division of Neuroscience and Behavioral Research, NIDA, March 7, 2003.

- Lecture: **Sex Differences in Nicotine Dependence**
  Guest lecture in the course, Psychology of Women, American University, April 7, 2003.

- Keynote address: **Gender-based Approaches in Drug Abuse**
  Alcohol & Drug Problems Association of North America National Women's Conference, Buffalo, NY, and Rockville, MD, September 14–16, 2003.

- Lecture: **Sex Differences in Nicotine Dependence**
  NIDA's Nicotine Workgroup, October 22, 2003.

- Keynote address: **Gender-based Approaches to Drug Abuse**
  Conference on Women and Mental Health, Baltimore, MD, May 17, 2004.

- Workshop discussant in symposium: **Sex, Drugs and No Rock 'N Roll**
  College on Problems of Drug Dependence, San Juan, PR, June 12-17, 2004.

- Plenary address: **Gender Differences in Drug Abuse Across the Life Span**
  Conference, Women Across the Life Span: A National Conference on Women, Addiction and Recovery, sponsored by the Center for Substance Abuse Treatment,

Substance Abuse and Mental Health Services Administration, Baltimore, MD, July 12-13, 2004.

And, finally, the importance of research on women and sex/gender differences and scientific findings from this research is often featured in talks given by NIDA's Director, Dr. Nora Volkow. Below are examples from presentations in 2003 and 2004.

- **Drug Abuse and Other Compulsive Behavior: Insights from Neuroimaging**
  Wisconsin Women's Health Foundation Advisory Board, Bethesda, MD, December 3, 2003.
- **Neuroimaging the Contrast: Cocaine-Addicted Men vs. Women**
  American College of Neuropsychopharmacology (ACNP) annual meeting, San Juan, PR, December 10, 2003.
- **Gender Matters in Drug Abuse and Addiction**
  Presentation for the U.S. Assistant Surgeon General and students, Rockville, MD, February 24, 2004.
- **The Neurobiology of Nicotine Addiction**
  Presentation at First Breath Wisconsin Women's Health Foundation Training Conference, Madison, WI, July 30, 2004.
- **Effects of Nicotine on Fetal Brain Development**
  Presentation at First Breath, Wisconsin Women's Health Foundation Training Conference, Madison, WI, July 30, 2004.
- **Research Advances in Drug Abuse and Addiction**
  Meridian International Center's Professional Women's Series, Washington, DC, November 3, 2004.
- **Progress and Priorities at the National Institute on Drug Abuse**
  Presentation at the NIH ORWH Advisory Committee on Research on Women's Health, Bethesda, MD, November 18, 2004.

APPENDIX A

Evaluation of the ORWH's First Ten Years

Acknowledgments

On behalf of the Office of Research on Women's Health (ORWH), I am pleased to share with you the results of the Evaluation of the ORWH's First Ten Years. The study is one of the most comprehensive evaluations of a program within the Office of the Director, National Institutes of Health (NIH). It represents a collaborative effort on the part of many dedicated individuals.

The members of the evaluation advisory committee played a key role in improving the algorithms for identifying research relevant to women's health, assessing the preliminary results of the evaluation, and providing the ORWH with recommendations for monitoring future progress. The committee was composed of senior administrators representing a variety of NIH components and one member who provided an external viewpoint. The names and affiliations of the members of the evaluation advisory committee are presented in Appendix A.

Several ORWH administrators and staff contributed a significant amount of time to the project. I acknowledge with gratitude the assistance of Joyce Rudick, who served as the task leader for the study, and Margaret Chesney, Ph.D., who served as a visiting scientist at the ORWH and played a major role during the feasibility study and launch of the full-scale evaluation.

The ORWH contracted with Carlyn Consulting to design and conduct the evaluation. Marcia Carlyn, Ph.D., served as the project director. The evaluation team included Mary Look, Ph.D. (Senior Vice President, Macro International Inc.), June Bray, Ph.D. (a senior research consultant with expertise in women's health), and Vaishali Joshi (a programmer/analyst at QRC Division of Macro International Inc.). An important factor in the success of the study was QRC's extensive experience working with the NIH databases used in the evaluation.

I am very thankful to all of the above-mentioned individuals for their significant contributions to this important project.

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

Executive Summary

The Office of Research on Women's Health (ORWH) is the focal point for women's health research at the National Institutes of Health (NIH). It was established in September 1990 to serve as a catalyst in mobilizing the different NIH institutes and centers (ICs) and the broader scientific community to address gaps in knowledge related to women's health. Located within the Office of the Director, the ORWH is responsible for working in partnership with the various ICs to address a threefold mandate to:

- Promote research related to diseases, disorders, and conditions that affect women;
- Ensure that women are appropriately included as subjects in biomedical and behavioral research studies supported by the NIH; and
- Develop opportunities and support for the recruitment, retention, reentry, and advancement of women in biomedical careers.

Under the NIH Revitalization Act of 1993, Congress codified the ORWH's mission and included directives that expanded its leadership role in identifying and promoting research on women's health. The act required the establishment of two committees to assist the ORWH Director: a broad-based external Advisory

Committee on Research on Women's Health (ACRWH) and an internal Coordinating Committee on Research on Women's Health (CCRWH) composed of IC directors or their designees.

Like other program offices within the Office of the Director, ORWH does not have direct funding authority for research studies but rather transfers funds to individual ICs to encourage and support specific projects. Although ORWH is a relatively small office, its staff and budget have grown substantially since its inception. The number of full-time-equivalent staff increased from three to 16 and its annual budget increased from $1.5 to $20.4 million from FY 1991 to FY 2000. These resources, along with resources provided by the various ICs to promote research on women's health, have been instrumental in helping the ORWH pursue its mandate.

In the fall of 2000, the ORWH celebrated its 10th anniversary. During its first decade, the office defined its primary goals, emphasized strategic planning, and used a variety of approaches to help achieve its goals. Given the tenure of the ORWH and the continuing strong interest in research on women's health, the ORWH Director decided in 2001 that a comprehensive evaluation of the ORWH's first 10 years was needed to assess the progress that had been made, enhance future planning, and contribute to program accountability. A two-phase program evaluation was begun in May 2001, with phase 1 consisting of a feasibility study to determine the design and data collection strategy for a comprehensive evaluation. The present phase 2 study, which was implemented during 2002-2003, incorporated the phase 1 design and the recommendations of ORWH staff and an *ad hoc* evaluation advisory committee. The study is one of the most comprehensive evaluations ever conducted of a program within the Office of the Director, NIH.

Evaluation Design

This study was primarily an outcome evaluation aimed at determining the extent to which the ORWH's intermediate and long-term goals were achieved during its first 10 years (FY 1991 through FY 2000). The design also included elements of a process evaluation in its examination of the major activities conducted by the office to achieve these goals and the output produced. The conceptual framework for the evaluation (shown in Exhibit 1) illustrates how the ORWH's activities, most of which involved collaborations with ICs and organizations outside the NIH, were expected to influence the achievement of its goals.

The following strategies were employed to collect data on the different variables in the conceptual framework and answer the study questions:

- Analyzing the content of ORWH publications and program records.
- Analyzing the content of other documents produced by the NIH and external organizations.
- Obtaining information from websites maintained by the ORWH and other NIH components.
- Performing queries of two large NIH databases, the Consolidated Grant Applicant File (CGAF) and the Computer Retrieval of Information on Scientific Projects (CRISP) system, using analytical methodologies and algorithms developed and pilot-tested in phase 1.
- Developing an ORWH activities database to summarize key information on the major program activities conducted by the office during the 10-year period.
- Holding discussions with the ORWH Director and staff, other NIH personnel, and members of the evaluation advisory committee.

Four broad study questions were addressed, with most of the data analyses comparing performance during FY 1999-2000 with performance during the baseline period FY 1989-1990 (prior to the establishment of the ORWH). Wherever possible, graphs and tables were used to summarize the results, and standard statistical tests (chi-square tests) were conducted to assess the significance of the findings. The study's primary focus was to assess the extent to which the ORWH's

goals had been achieved during the 10-year period; it was not designed to determine whether there was a direct cause-and-effect relationship between specific ORWH activities and goal achievement given the difficulty in eliminating other factors that undoubtedly contributed to the achievement of these broad goals.

Findings

Study Question 1: What were the ORWH's major activities during its first 10 years and how were they implemented?

Study Question 1 involved identifying the primary activities that the ORWH conducted during FY 1991-2000, examining how they were implemented, and assessing the output produced during this period. The ORWH activities database that was designed for the evaluation proved to be essential in understanding the nature and extent of the different activities conducted by the office.

The results showed that in addressing its mandate, the ORWH actively participated in over 1,700 program activities during its first decade, a noteworthy record for a relatively small program. Six major types of activities were identified:

1) Interacting with scientists, professional organizations, and advocacy groups to exchange information on issues related to women's health research.

2) Developing a research agenda on women's health for the NIH community.

3) Collaborating with NIH ICs to promote women's health research and career opportunities.

4) Co-funding NIH research studies on women's health and career development awards.

5) Overseeing implementation of the NIH policy on the inclusion of women and minorities in study populations.

6) Promoting women's health research through the dissemination of scientific publications, policy documents, and educational materials.

The evaluation found that the ORWH was exceptionally proactive throughout the decade in reaching out to a broad range of scientists, professional organizations, and advocacy groups to exchange information and solicit recommendations for achieving common goals. Altogether, nearly 250 research conferences, seminars, and workshops were sponsored or co-sponsored by the ORWH during this period. After reaching early consensus on a comprehensive NIH-wide research agenda on women's health, the ORWH worked closely with the different NIH ICs to encourage them to support research on high-priority women's health topics and address other aspects of its mandate. The office organized 16 trans-NIH committees/task forces, many of which are still meeting on a regular basis. During its first 10 years, the ORWH also co-sponsored 48 Requests for Applications (RFAs) and Program Announcements (PAs) in collaboration with one or more ICs.

The study also found that the ORWH co-funded over 1,000 NIH research studies and over 125 career development awards during its first 10 years, providing nearly $95 million to ICs to support specific projects. The research studies focused primarily on the topics in the NIH research agenda on women's health and the highest priority topics were generally given the most attention, demonstrating the effectiveness of the ORWH's strategic planning and agenda development process. In addition, five new NIH programs were developed by the ORWH to address the numerous barriers faced by women pursuing biomedical careers. With respect to the NIH inclusion policy, the ORWH initiated and supported over 90 activities aimed at ensuring that women and minorities were appropriately included as subjects in clinical research studies supported by the NIH. In addition, the ORWH developed and/or co-sponsored over 120 scientific publications, policy documents, and educational programs to promote women's health research and career opportunities.

Given ORWH's limited staff and budget, its strong emphasis on interdisciplinary collaboration was regarded as essential for the achievement of its goals. In pursuing its activities, the ORWH worked closely with

the ACRWH, CCRWH, IC representatives, senior staff in other government agencies, scientists and advocacy groups throughout the country, and other interested parties.

Study Question 2: To what extent were the ORWH's intermediate goals achieved during its first 10 years?

1) *More RFAs and PAs to stimulate and expand research on women's health*. The number of official IC notices (RFAs and PAs) that invited grant applications addressing women's health issues increased by 143 percent, which was much higher than the 20 percent overall increase in NIH RFAs and PAs from FY 1989-1990 to FY 1999-2000. An additional content analysis was conducted to determine the number of RFAs and PAs that specifically mentioned a need for research on sex/gender differences in a particular area (going beyond the standard NIH language). The results showed that the number of RFAs/PAs encouraging research on sex/gender differences also increased significantly over the 10-year period, rising from an average of five to 41 per year.

2) *Increased NIH funding for women's health research*. NIH research funding specific to women's health increased by 60 percent from FY 1993 to FY 2000, which was slightly higher than the 57 percent overall increase in NIH research funding during the period. The results were based on budget figures reported by individual ICs for research specific to women, to men, and to both women and men. However, given the inherent difficulties in determining non-overlapping budget allocations for interdisciplinary research specific to women, the results should be interpreted with caution.

3) *More NIH grant applications involving women's health research*. The number of research project grant (RPG)[1] applications involving women's health research increased by 48 percent during ORWH's first 10 years, which was nearly twice the 25 percent overall increase in the number of RPG applications during the period. The greatest gains were found for R03 grants (small research grants which are often awarded to new investigators), P01 grants which involve an interdisciplinary team of investigators, and U01 cooperative agreements.

4) *More women receiving postdoctoral fellowships to pursue biomedical careers*. The number of postdoctoral F32 fellowship applications submitted by women increased by 4 percent during the period, which was much greater than the 17 percent decrease in the number of applications from men. The number of F32 fellowships awarded to women increased by 10 percent, compared to a 3 percent decrease in the number of awards to men. With respect to both applications and awards, F32 fellowships had the highest proportion of female PIs of all the NIH grant mechanisms investigated in the ORWH evaluation. Although at the end of the ORWH's first 10 years a majority of NIH postdoctoral fellows were male, the proportion of females was substantial (42 percent). Perhaps more importantly, the results indicate that by FY 1999-2000, a large number of female scientists were approaching the end of the academic pipeline and would soon be ready to begin their careers as independent research scientists.

5) *More women applying for NIH research grants*. The number of RPG applications submitted by women increased by 56 percent during the ORWH's first 10 years, which was much higher than the 18 percent increase in applications from men. The percent of female applicants increased for every type of grant analyzed, although there was considerable variance among the different types of grant mechanisms. However, despite the sizeable gains, only 25 percent of the RPG applications and 13 to18 percent of the P30, P50, and T32 applications were submitted by female PIs in FY 1999-2000.

[1] Research project grants (RPGs) are the most common type of investigator-initiated research grants awarded by NIH; they include activity codes R01, R03, R15, R21, R29, R33, R37, R55, P01, P42, U01, and U19 (excluding NLM grants, FIC grants for FY 1989-1990, and NCRR grants for FY 1989).

Study Question 3: To what extent were the ORWH's long-term goals achieved during its first 10 years?

1) *More NIH-sponsored research on women's health in high-priority areas*. The number of RPG awards involving the 37 high-priority areas of women's health increased by 70 percent, which was substantially higher than the 56 percent overall increase in RPG awards from FY 1989-1990 to FY 1999-2000. An additional analysis of project titles found that the number of RPG awards having titles relevant to women's health also increased significantly (by 79 percent). Given the importance of this ORWH goal, the results were especially heartening.

2) *More women successfully competing for NIH research grants*. The number of RPGs awarded to women increased by 84 percent, which was considerably higher than the 49 percent increase in awards to men. The percent of awards to female PIs increased for every type of grant analyzed and female applicants had approximately the same probability of success as male applicants in FY 1999-2000, indicating there was no systemic bias against female applicants. However, despite all of these gains, only 23 percent of the RPG grants and 13 to 17 percent of the P30, P50, and T32 grants were awarded to female PIs in FY 1999-2000. These results and the findings for Intermediate Goal 5 underscore the importance of increasing the number of female investigators who apply for NIH grants.

3) *High percentage of participants in ORWH career development programs becoming independent research scientists*. Of the 26 individuals who participated in the initial ORWH Re-entry Program during FY 1992-1994, 88 percent had published in peer-reviewed journals after finishing the program, 73 percent had secured a permanent research position, 54 percent had applied for an NIH grant, 19 percent had received an NIH grant, and 27 percent had obtained some type of external research funding by FY 2001. The percentages were higher than the performance targets set by the ORWH, although the 27 percent success rate in obtaining external research funding was disappointing. The results illustrate how challenging it can be to obtain such funding (particularly an NIH grant), even for fully trained biomedical scientists intent on re-establishing their research careers.

4) *Increased institutional commitment to women's health research*. The number of NIH-supported institutions with major research and training centers involving women's health increased by 87 percent, from an average of 15 per year in FY 1989-1990 to 28 per year in FY 1999-2000. The evaluation also found that a relatively high proportion of these large institutional grants had female PIs. For example, 33 percent of the principal investigators of P01 grants involving women's health were female, compared to 15 percent of the PIs of all P01 grants awarded in FY 1999-2000.

5) *Stronger evidence that women and minorities are being appropriately included as subjects in clinical research supported by NIH*. Substantial evidence was found that the ORWH's efforts and those of other NIH offices and ICs were effective in strengthening the NIH's inclusion policy. The GAO report issued in 2000 concluded that the NIH had made significant progress since 1990 in implementing a stronger policy for including women in clinical research and the "ORWH played a key role in implementing the inclusion guidelines." From FY 1995 to FY 2000, the percent of new NIH extramural grant applications involving human subjects that were found to have unacceptable sex/gender and/or minority inclusion fell from 7.3 to 5.6 percent, demonstrating an improved level of investigator compliance with the NIH's inclusion policy. In addition, the number of NIH-supported research studies that examined sex/gender and/or racial/ethnic differences in disease etiology and treatment increased from an average of 101 to 398 per year (an increase of 394 percent) during the ORWH's first

10 years. An unexpected finding was that nearly all of these studies focused on either sex/gender or racial/ethnic differences; only a small fraction of the studies (3 percent in FY 1999-2000) examined differences in both areas.

Study Question 4: Which areas of NIH-sponsored women's health research grew the fastest during the 10-year period?

The evaluation found that for 29 of the 37 high-priority research topics (78 percent), the number of RPGs involving the topic grew by more than the overall increase in RPG awards during the period. Also, for 31 of the 37 topics (84 percent), the number of different ICs funding research on the topic increased. The following eight topics had exceptionally large increases in RPGs ($p < .001$): cultural and lifestyle factors, breast cancer, adolescent health, HIV/AIDS, behavioral change and risk-taking behavior, violence, menopausal hormone therapy, and menopause (in general).

Comparing the broader research areas, the largest increases in new RPG awards were found in behavioral research, aging, cancer, and infectious diseases and immune disorders. The research area that had the lowest growth in terms of new RPG awards was reproductive and maternal health, which was unexpected since the ORWH had co-funded nearly 400 research studies involving reproductive and maternal health during the 10-year period.[2] Overall, the findings were very positive and consistent with the earlier findings for Long-Term Goal 1.

Recommendations

After reviewing the evaluation findings, the evaluation advisory committee concluded that the NIH had clearly increased its commitment to women's health research during the 1990s. Taken together, the findings indicate that the ORWH's strong emphasis on collaboration and strategic planning, its development of a comprehensive trans-NIH research agenda for women's health, and its success in leveraging funds to encourage high-priority projects were major factors in raising the awareness of women's health across the NIH. The result was a gradual culture change that had a very positive impact on the achievement of the ORWH's goals. There was consensus that the ORWH's approach could well serve as a model for other interdisciplinary programs pursuing trans-NIH issues and goals.

While emphasizing that a great deal of progress had been made, the members of the advisory committee also felt that there was more work to be done. To track future progress, the committee recommended that the ORWH take the following steps:

1) *Ensure that the NIH research agenda on women's health is updated on an annual basis*. Consider developing an improved "master list" of diseases, disorders, and conditions affecting women which minimizes overlap among the topics while recognizing the multisystemic nature of many of the diseases. Using such a master list and a methodology similar to the one used in the evaluation, identify the highest priority research topics in accordance with the recommendations of the CCRWH research subcommittee, ACRWH members, and the working groups participating in recent agenda-setting conferences sponsored by the ORWH.

2) *For each high-priority research topic, continue to track the average number of new RPGs awarded per year involving that topic by employing the CRISP methodology developed for the evaluation*. Given the increasing importance of interdisciplinary research, consider expanding the methodology to include non-RPG research center awards, such as P30, P50, M01, U10, U54, M01, and G12 grants. Examine the feasibility of using CRISP analyses for grant applications as well as awards after the

[2] A subsequent analysis revealed that the lack of expansion in RPGs involving reproductive and maternal health was probably due to the strategy employed by the National Institute of Child Health and Human Development (NICHD) during this period to develop a broad network of maternal–fetal medicine units and reproductive health centers using non-RPG grant mechanisms (primarily U10 and U54 cooperative agreements and K12 awards), with nearly $16 million of co-funding provided by the ORWH.

IMPAC II system is expanded to include research abstracts for applications.

3) *Continue to track the number of RPG, P30, P50, F32, and T32 grant applications submitted by female PIs and the number awarded to female PIs*, summarizing the results in tables and pie charts, and consider expanding the CGAF methodology to include non-RPG career development awards and collaborating investigators (co-PIs) of major research center grants.

4) *Continue to track the number of NIH-supported institutions with major research and training centers involving women's health by analyzing CGAF project titles*.

5) *Continue to monitor ORWH activities, expanding the ORWH activities database and updating the graphs showing trends through time for different types of activities*. Develop a logging system within the office to document ORWH activities on a daily or weekly basis to ensure that all outreach projects and other major activities are counted.

6) *Post the results of the above analyses on the ORWH website and include the results in the ORWH's biennial reports* so that IC staff and others interested in particular research topics and career development programs can track progress in a timely way to determine whether specific strategies should be revised.

7. *Continue to promote the NIH inclusion policy* and encourage the various ICs, including their intramural researchers, to support more studies examining sex/gender and racial/ethnic differences in disease etiology and treatment.

8) *Conduct a followup evaluation in FY 2006 to assess the ORWH's progress during the 5-year period from FY 2001 to FY 2005*. Include an analysis of the new investigators who participated in the ORWH's Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program and those who received the ORWH Transitional Career Development Awards in Women's Health Research during the first 2 years of each program.

In conclusion, the Evaluation of the ORWH's First 10 Years was a comprehensive assessment of the progress that was made from FY 1991 to FY 2000 in achieving the ORWH's intermediate and long-term goals. The findings were generally positive and quite remarkable for a relatively small program office. The extensive amount of data collected for the evaluation will serve as a valuable resource in tracking the ORWH's future progress. In addition to contributing to program accountability, the study included the development of new analytical methodologies designed to be useful to the ORWH as well as other IC administrators and researchers interested in assessing changes in an NIH research portfolio over a specified time period. It is hoped that all those who manage, fund, or provide other support for projects involving women's health will be encouraged by the evaluation results and find them helpful in developing and improving a variety of interdisciplinary research programs.

APPENDIX B

Ad Hoc Research Subcommittee of the Coordinating Committee on Research on Women's Health, 2003

Representative	*Title*	*Institute or Center*
Donna Vogel, M.D., Ph.D. Co-chair	Senior Program Management Officer	NCI
David Robinson, Ph.D., Co-chair	Deputy Director, Division of Heart and Vascular Diseases	NHLBI
Mary Blehar, Ph.D.	Program Director	NCI
Patricia Bryant, Ph.D.	Director, Behavioral and Social Science Research Program	NIDCR
Paul Coates, Ph.D.	Director, Office of Dietary Supplements	OD/ODS
Elaine Collier, M.D.	Assistant Director for Clinical Research	NCRR
Eleanor Hoff, Ph.D.	Health Science Policy Analyst	NIDDK
Sooja Kim, Ph.D., R.D.	Chief, Endocrinology, Metabolism, Nutrition and Reproductive Sciences Integrated Review Group	CSR
Cheryl Kitt, Ph.D.	Director, Extramural Program	NIAMS
Anna T. Levy, M.S.	Deputy Director, Office of Women's Health	NCI
Pamela A. Marino, Ph.D.	Program Director	NIGMS
Ted Trimble, M.D., M.P.H.	Head, Gynecologic Cancer Therapeutics & Quality of Cancer Care	NCI
Cora Lee Wetherington, Ph.D.	Women & Gender Research Coordinator	NIDA
ORWH Liaisons		
Lisa Begg, R.N., Dr.P.H.	Director of Research Programs	OD/ORWH
Loretta Finnegan, M.D.	Medical Advisor	OD/ORWH

Ad Hoc Research Subcommittee of the Coordinating Committee on Research on Women's Health, 2004

Representative	*Title*	*Institute or Center*
Elaine Collier, M.D. Co-chair	Assistant Director for Clinical Research	NCRR
Elaine Hoff, Ph.D. Co-chair	Health Science Policy Analyst	NIDDK
Frank Bellino, Ph.D.	Deputy Associate Director, Biology of Aging Program	NIA
Mary Blehar, Ph.D.	Program Director	NCI
Maria Teresa Canto, D.D.S., M.S., M.P.H.	Director, Epidemiology Research Program	NIDCR
Carolyn Deal, Ph.D.	Chief, Sexually Transmitted Diseases Branch	NIAID
Karen A. Johnson, M.D., Ph.D., M.P.H.	Chief, Breast and Gynecologic Cancer Research Group, Division of Cancer Prevention	NCI
Sooja Kim, Ph.D., R.D.	Chief, Endocrinology, Metabolism, Nutrition and Reproductive Sciences Integrated Review Group	CSR
Cheryl Kitt, Ph.D.	Director, Extramural Program	NIGMS
Anna T. Levy, M.S.	Deputy Director, Office of Women's Health	NCI
Pamela A. Marino, Ph.D.	Program Director	NIGMS
Merle Myerson, M.D., Ed.D.	Cardiologist & Medical Officer	NHLBI
Mary Frances Picciano, Ph.D.	Senior Advisor, Office of Behavioral & Social Sciences Research	OD/OBSSR
Cora Lee Wetherington, Ph.D.	Women & Gender Research Coordinator	NIDA
ORWH Liaison/Ad Hoc Members		
Lisa Begg, R.N., Dr.P.H.	Director of Research Programs	OD/ORWH
Loretta Finnegan, M.D.	Medical Advisor	OD/ORWH
Charisee Lamar, Ph.D., M.P.H.	Program Director	NIAMS

APPENDIX C
Office of Research on Women's Health Research Summaries, 2003

Adolescent Health

▶ Title: *Mothers Living with HIV and Their Adolescent Children* NIMH
P.I.: Mary Jane Rotheram-Borus, Ph.D.
Institution: The Regents of the University of California, Los Angeles
Grant No.: 1 R01 MH068194-01A1
Study Type: Clinical
Amount: $300,000

The number of parents living with HIV is significant and rising, as the length and qualify of life of persons living with HIV has increased. When mothers become infected with HIV, they face not only the challenges associated with their infection, but their entire family is affected, with long-term negative outcomes for themselves and their children. This research team completed previous randomized controlled trials with parents with HIV and their children and young people living with HIV, suggesting the benefits of improving coping skills, family relationships, and dealing with illness-related tasks (e.g., disclosure). The proposed trial builds on these results to implement prevention services in treatment settings to improve long-term outcomes for mothers and their adolescent children, gathering evidence to inform dissemination. All mothers living with HIV (MLH) with adolescent children at three sites in the Los Angeles Pediatric AIDS Consortium (n = 400 MLH) will be randomly assigned within site to one of two conditions: 1) a four-module intervention (16 sessions) and access to booster sessions as needed (n = 200 MLH; 320 youth); or 2) a standard care condition (n = 200 MLH; 320 youth). The MLH's intervention will address improved health behaviors (Module 1), parenting skills and family relationships (Module 2), reduced transmission acts and problem behaviors (Module 3), and improved mental health (Module 4). For youth who know the MLH's serostatus, the intervention will be delivered in conjunction with three of the MLH's modules and address coping with parental illness (MLH's Module 2), reducing multiple problem behaviors (Module 3), and improving mental health (Module 4). Youth whose MLH die will receive a fourth module to cope with parental bereavement and to set new life goals. The impact will be assessed over 2 years (recruitment, 3, 6, 12, 18, and 24 months), in a design that is a blend of an efficacy and effectiveness trial. The outcomes will be the MLH's health status, and youth and MLH's parent-child relationships, problem behaviors, and mental health symptoms. In addition, youth's developmental outcomes will be monitored. In order to assess the uniqueness of the impact of HIV, the investigators will assess a cohort of parents and adolescents in a neighborhood control group (n = 200 mothers; 320 youth) matched for age, gender, and ethnicity on the same measures.

Aging

▶ Title: *Aging of Brain: Effects of Prenatal Nutrition* NIA
P.I.: Jan Blusztajn, Ph.D.
Institution: Boston University, MA
Grant No.: 2 P01 AG09525-11
Study Type: Basic
Amount: $100,000

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

▶ Title: *A Fall Prevention Program for High-risk Elderly Women* NINR
P.I.: Jean F. Wyman, Ph.D., R.N.
Institution: University of Minnesota, Minneapolis
Grant No.: 5 R01 NR005107-03
Study Type: Clinical
Amount: $100,000

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

▶ Title: *Role of Estrogen in the Pathogenesis of Tubulointerstitial Disease in Aging* NIA
P.I.: Christine Maric, Ph.D.
Institution: Georgetown University, Washington, DC
Grant No.: 1 R03 AG22233-01
Study Type: Basic
Amount: $77,600

Despite the most recent report on the risks of combined estrogen (E2) and progestin therapy on cardiovascular disease, there is still no evidence to suggest that E2 alone is not protective in these disease processes. This stresses the importance of further studies to determine the precise role of E2 in mediating systemic and cellular function that may adversely be regulated in age-related disease. Renal disease is an underlying and/or contributing factor to cardiovascular and other age-related diseases. Age-related renal disease is associated with glomerulosclerosis and tubulointerstitial fibrosis; however, the factors mediating these processes have thus far not been examined. Based on preliminary data showing that the renal renin–angiotensin system (RAS) is downregulated with ovariectomy, it is hypothesized that the protective role of E2 is partially mediated by downregulation of the RAS. Previous studies also show that expression of enzymes involved in nitric oxide (NO) synthesis is downregulated with ovariectomy, and it is hypothesized that the protective role of E2 will be mediated by upregulation of NO synthesis. Both Ang II and NO regulate cell proliferation and extracellular matrix (ECM) metabolism, the two major processes that are adversely affected and contribute to the development of glomerulosclerosis and tubulointerstitial fibrosis. The overall hypothesis of this research is that E2 regulates the RAS and nitric oxide pathways and that the increased responsiveness of their specific target cells (proximal tubule and renal interstitial fibroblasts) contribute to the pathogenesis of age-related tubulointerstitial injury. Specific Aim 1 will examine the functional changes in the aging kidney, due to abnormal regulation of the RAS and NO pathways: renal expression of the components of the cell-specific RAS and NOS will be measured by real-time PCR and Western analysis. Specific Aim 2 will examine the structural changes in the aging kidney, due to of the abnormal regulation of the RAS and NO pathways: tissue morphological changes, cell proliferation, and ECM metabolism will be examined by immunohistochemistry, light microscopy, Western analysis, and zymography. Knowledge gathered from these studies will contribute to our overall understanding of processes that are adversely affected with aging and may lead to development of novel therapeutic strategies to prevent age-related disease in women.

▶ Title: *Relaxation Therapy for Alzheimer Caregivers* NINR
P.I.: Sharon Lewis, Ph.D., R.N.
Institution: University of Texas Health Science Center, San Antonio
Grant No.: 2 R01 NR04345-06A1
Study Type: Clinical
Amount: $99,999

Aging baby boomers, longer life spans, and rising levels of Alzheimer disease and related disorders (ADRD) will result in a major caregiver crisis in the near future. Although family caregivers perform an incredibly valuable service, they do so at a considerable cost to themselves, both emotionally and physically. Effective stress management programs for caregivers are vitally needed to 1) help them decrease their stress, 2) improve their emotional and physical health, and 3) empower them to gain control of their lives. The overall goal of this randomized controlled clinical trial is to determine the effectiveness of a stress-busting program (SBP) for caregivers of patients with ADRD. Specific research aims include: 1) to prospectively determine the effects of a SBP compared to a standard support group (SSG) on quality of life, immune response, and relaxation response using bioinstrumentation to measure muscle tension,

electrodermal response, skin temperature, blood volume pulse, and blood pressure; and 2) to assess the effectiveness of SBP or SSG for adult children caregivers as compared to spousal caregivers based on quality-of-life measurements, immune parameters, and relaxation response. Subjects will be tested at baseline, at completion of 4 and 8 weeks of a SBP or SSG, and at 2- and 4-month follow-up sessions to determine the long-term effectiveness of the intervention. The proposed 8-week multimodal SBP will focus on stress management, relaxation therapy, and education related to stress and relaxation, managing challenging behavior, depression, coping strategies, positive thinking, and taking time for oneself. The setting will be an educational support group. A repeated measures design will be used to determine the effectiveness of SBP compared to SSG. Outcomes will be measured using psychosocial instruments as well as state-of-the-art science technology, including bioinstrumentation and immune parameters to measure biological responses. The SBP is proposed as a way to decrease the level of stress experienced by caregivers and teach them effective coping strategies. If SBP is found to be more effective than SSG in decreasing stress, improving quality of life, promoting relaxation, and/or enhancing immunocompetence in family caregivers, these findings could have important clinical significance for providing a cost-effective health promotion strategy for a group of people who experience tremendous ongoing stress.

▶ Title: *Custodial Grandparents and Religion and Spirituality* NIA
P.I.: Martha Crowther, Ph.D.
Institution: University of Alabama, Tuscaloosa
Grant No.: 1 R03 AG 022650-01
Study Type: Clinical
Amount: $61,800

This proposal is to study the reduction of health disparities among older persons and populations by conducting research to disentangle the effects of socioeconomic status, social and environmental factors, health behaviors, and race and ethnicity on health. There has been a steady increase in the number of African American custodial grandparents. Many grandparent caregivers experience stress, decreased social and economic well-being, and reduced physical health as a result of caregiving. As interest in this area grows, questions as to methods grandparents use to cope with the stress of caregiving increase. There is a paucity of data available on the use of religious and spiritual practices among grandparents who raise their grandchildren. Preliminary results suggest that African American custodial grandparents are very religious and spiritual, and that religiosity and spirituality may serve as coping mechanisms for grandparents who are primary caregivers for their grandchildren. Research in the area of cognition and aging suggests that there may be differences in the cognitive abilities of those actively involved in social activities. Preliminary results suggest that older African Americans that gave support have higher levels of everyday problem-solving abilities. The primary aim of this study is to examine the impact of the social activities many custodial grandparents engage in which include religious activities and activities surrounding raising their grandchildren as a protective factor against the stressors associated with caregiving and a method to enhance their cognitive abilities. While designed primarily to assess the relation between the stressors of custodial grandparenting, religion/spirituality and cognition, the proposed study has clinical and policy implications. Clinically, the results of the proposed study could help identify topics to be addressed in grandparent caregiver support groups, such as problem-solving skills and coping skills. It will also aid in assessing the types of practical skills needed to provide care for others. In the realm of policy, the results of the current study could identify the areas of concern for grandparent caregivers, such as obtaining access to medical care for their grandchildren.

▶ Title: *Health, Illness, and Social Life at Older Ages* NIA
National Social Life Health and Aging Project
P.I.: Linda Waite, Ph.D.
Institution: Department of Sociology, Center on Aging, University of Chicago, IL
Grant No.: R01 AG021487-01
Study Type: Clinical
Amount: $250,000

It is well established that social support, particularly marriage, bolsters psychological and physical health as people age. Human sexuality constitutes one essential, but poorly understood, parameter of both healthy aging and social life at older ages. Physicians and public health policymakers lack a scientific base of information for advising older people or designing programs that might promote sexual health, support prolonged independence, relieve anxiety, prevent dysfunction or disease, or address current issues influencing intimate social and sexual relationships among older Americans. The Interactive Biopsychosocial Model (IBM) developed for this research is an extension of Engel's biopsychosocial model. Health is conceptualized as a function of biophysical and psychocognitive dynamics between individuals over time and incorporates social embeddedness in shaping that process. A nationally representative probability sample of 3,000 community-residing women and men ages 57 to 84 will be followed longitudinally in two waves over 5 years. We will oversample African American and Hispanic adults. Face-to-face interviews and biomarker collection will take place in respondents' homes. Data collection will elicit: 1) demographics; 2) social networks; 3) social and cultural activity; 4) physical and mental health, including cognition; 5) well-being; 6) illness; 7) medications and alternative therapies; 8) history of sexual and intimate partnerships; and 9) patient–physician communication regarding sexuality, sexual identity, functionality, desire, opportunity, and attitudes about sexuality and intimacy. Biomarker collection will include: height, weight, blood pressure, serum (glucose metabolism, HIV, hepatitis, syphilis), urine (gonorrhea, chlamydia, trichomonas), saliva (endocrine evaluation), and sensory testing (vision, hearing, touch, taste, smell). Three specific aims will be addressed: 1) describe health and health transitions of older community-residing Americans, 2) evaluate the relationship between health and older adult sexuality, and 3) examine sexuality within social networks and their sociocultural context.

Alcohol and Other Substance Abuse

▶ Title: *Alcohol, HIV-risk Behaviors, and Sexual Victimization* NIAAA
P.I.: Maria Testa, Ph.D.
Institution: Research Institute on Addictions, Buffalo, NY
Grant No.: 5 R01 AA12013-05
Study Type: Clinical
Amount: $50,000

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

▶ Title: *Effects of Smoked Heroin Across the Menstrual Cycle on Cessation* NIDA
P.I.: Suzette Evans, Ph.D.
Institution: Research Foundation for Mental Hygiene, New York, NY
Grant No.: 1 R01 DA016762-01
Study Type: Basic
Amount: $298,391

There is growing evidence that there are sex differences in response to drugs of abuse. However, only a limited number of studies in rodents have assessed whether there are sex differences in the reinforcing effects of opioids and the human data are sparse. Nevertheless, some of the sex differences observed can be attributed to cycling ovarian hormones in females. This proposal will parametrically evaluate the behavioral and reinforcing effects of smoked heroin across the menstrual cycle in normally cycling, adult female rhesus monkeys. Levels of estradiol (EST), progesterone (PRO), and luteinizing hormone (LH) will be routinely monitored, correlating changes in hormone levels to the behavioral effects of heroin. Exp. 1 will carefully characterize the time course of heroin blood levels across the menstrual cycle. Subsequently, heroin seeking and taking will be measured using a second-order schedule, choice and location preference procedures when the monkeys are not dependent (Exp. 2); and again (Exp. 4) when they are dependent on opioids; and the reinforcing effects of heroin will be measured using a Progressive Ratio procedure when the monkeys are not dependent (Exp. 3); and again (Exp. 5) when they are dependent on opioids. These experiments will provide valuable data about changes in the behavioral and reinforcing effects of heroin across the menstrual cycle when heroin is available under non-dependent and dependent conditions. In addition, this proposal will provide important information on the effects of self-administered opioids on the regulation of the menstrual cycle. The proposed studies will be the first to systematically evaluate these effects in female non-human primates.

▶ Title: *Gender Differences in Drug Abuse* NIDA
P.I.: Jill Becker, Ph.D.
Institution: The Regents of the University of Michigan, Ann Arbor
Grant No.: 2 R01 DA012677-04
Study Type: Basic
Amount: $291,889

The experiments proposed will utilize well-characterized animal models to study the neurobiological basis for gender differences in drug abuse. Neuroadaptations associated with sensitization to psychomotor stimulants are thought to play an important role in the process of addiction. Furthermore, gender differences in the behavioral and neurochemical effects of psychomotor stimulants have been repeatedly reported to occur in rodents and, more recently, in humans as well. In order to begin to understand gender differences in drug abuse, basic research on the role of gender and ovarian hormones in response to acute and repeated exposure to cocaine is an important next step. Research on the acute behavioral research to psychomotor stimulants indicates that treatment of female rats with the ovarian hormone estrogen is sufficient to induce changes comparable to the effects of the estrous cycle. There are two hypotheses to be tested. The first is that there are gender differences in behavior induced by repeated exposure to the psychomotor stimulants and gender differences in self-administration of cocaine. The second is that estrogen potentiates both the acute and sensitized response to cocaine in female rats enhancing these gender differences. In order

to begin to understand the underlying neurological bases for gender differences in cocaine addiction, there are two important factors that must be teased apart: 1) differences between males and females (independent of gonadal hormones); and 2) whether gonadal hormones in either males or females affect responses to cocaine. In humans these factors are intermingled because chronic cocaine use can disrupt and even cause cessation of a woman's menstrual cycle. In such women estrogen may play a role in acquisition of drug-taking behaviors but not in maintenance of these behaviors (since in women with amenorrhea the serum concentrations of estrogen are extremely low). On the other hand, more men than women abuse drugs and many boys begin using drugs prior to sexual maturation. The experiments proposed will allow the relative importance of gender vs gonadal hormones to be teased apart in animal studies investigating the effects on cocaine-induced psychomotor behavior and cocaine self-administration.

▶ Title: *College Women: The Alcohol and Victimization Link* NIAAA
P.I.: Kathleen A. Parks, Ph.D.
Institution: State University of New York at Buffalo, Amherst
Grant No.: R01 AA013986
Study Type: Clinical
Amount: $100,000

Victimization of young college women is a problem with potentially devastating consequences. Approximately 2 million women are new freshmen each year. A recent report estimates that 600,000 (13.3 percent) college students were assaulted because of drinking by other students over a 1-year period—6.4 percent of women reported being raped during their first year in school. Research findings indicate that 50 percent of sexual assaults in college involve alcohol. Based on these figures, 3.2 percent or 64,000 freshmen women experience an alcohol-related rape annually. Clearly victimization (nonsexual and sexual) is a significant alcohol-related problem on college campuses. The research proposed focuses on the longitudinal relationship between alcohol consumption and victimization among college women. The primary objectives of the proposed investigation are to: 1) describe the rates of alcohol consumption and alcohol-related victimization across 4 years of college attendance; 2) assess the temporal relationship between alcohol consumption and alcohol-related victimization (sexual and nonsexual, verbal and physical); 3) assess risk factors for experiencing victimization during college; and 4) assess primary (e.g., injury, psychological trauma) and secondary (e.g., academic, psychological) consequences of alcohol-related victimization. Two longitudinal research components will be used to achieve these research objectives. Component 1 involves a brief telephone survey, administered annually during the fall semester, of the drinking patterns, victimization, and other alcohol-related problems that occur in a cohort of women entering college for the first time during the Fall semester of 2003. Component 2 of the research involves an 8-week prospective assessment of drinking patterns and victimization experiences administered annually, during the Spring semester, to a sub-sample of women randomly selected during Year 1 from Component 1 participants. Component 2 will use state-of-the-art technology (interactive voice response) to collect daily data on alcohol consumption and any victimization that occurs. Event-based measures will be used to provide detailed data on victimization experiences. This research is innovative in the use of long- and short-term measures, within a longitudinal design, to assess alcohol-related victimization of college women.

▶ Title: *Reducing Alcohol and Risks Among Young Females* NIAAA
P.I.: Lydia N. O'Donnell
Institution: Education Development Center, Inc., Newton, MA
Grant No.: 1 R01 AA014515-01
Study Type: Clinical
Amount: $150,000

An intervention study will be undertaken to characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African American and Latina adolescent females who are at high risk for HIV, AIDS, and other infections. Past research by the investigative team has documented that nearly 10 percent of females in our target population are at risk in 7th grade, and more than half by the spring of 10th grade. Although alcohol use is more comparable with national figures, the combination of early alcohol and risky behavior is troubling, yet underaddressed by existing interventions. This randomized experiment will test a theoretically derived and empirically grounded "selective" intervention that specifically targets high-risk young adolescent females. The intervention builds upon a promising strategy for influencing adolescents: parent education. Three parenting mechanisms shown to influence adolescent risk behavior will be targeted: parental monitoring, household rule setting, and communication.

Cancer

▶ Title: *Clinical Trials of Two Human Papillomavirus-like Particle Vaccines* NCI
P.I.: Douglas R. Lowy, M.D.
Institution: National Cancer Institute, Bethesda, MD
Grant No.: 1 Z01 BC09052
Study Type: Clinical
Amount: $600,000

Worldwide, cervical cancer annually accounts for over 400,000 incident cases, resulting in approximately 200,000 deaths. The impact of this disease is particularly devastating in developing countries where women are medically underserved and access to Pap smear screening is not readily available. To address this major issue in women's health, the NCI and the Office for Research on Women's Health is launching a large, double-blinded, randomized clinical trial to evaluate whether vaccination with the bivalent human papillomavirus (HPV)16/18 VLP-based vaccine developed at the NCI and manufactured by GlaxoSmithKline will protect against the development of histopathologically confirmed, incident CIN2+ (cervical intraepithelial lesion grades 2/3), adenocarcinoma *in situ*, and invasive cervical cancer. This pivotal efficacy trial will be conducted in Costa Rica, an area with high rates of cervical cancer. Approximately 20,000 young women will be invited to join the trial, with 12,000 to 15,000 women expected to participate. Eligible women who agree to participate will be administered three doses of either a control vaccine or the HPV 16/18 VLP vaccine over a 6 month period and will be followed for 4 years. The trial is expected to extend through 2009. It is hoped that results from this effort will support licensure of a prophylactic HPV16/18 vaccine that protects against the development of HPV16/18-induced cervical cancer and its precursors.

▶ Title: *RCT of Plant-based Diet in Breast Cancer Recurrence* NCI
P.I.: John P. Pierce, Ph.D.
Institution: The Regents of the University of California, San Diego
Grant No.: 1 R01 CA 069375-06
Study Type: Clinical
Amount: $100,000

This proposal is to complete and close out the Women's Healthy Eating and Living (WHEL) Study, an ongoing multicenter (seven clinical sites), randomized, controlled trial examining the hypothesis that a plant-based dietary pattern affects additional breast cancer events and mortality. The study has enrolled 3,109 women who were within 4 years of a primary diagnosis of Stage I (≥ 1 cm), Stage II, and Stage IIIA breast cancer and who had completed standard therapy. The study uses a behavior-change-theory-driven comprehensive and tailored intervention to motivate intervention group participants to substantially increase daily consumption of vegetables, fruit, and fiber while reducing fat in a dietary pattern that should result in a large increase in circulating carotenoids. The study includes regular measures of self-reported dietary and supplement intake, personal habits, quality of life, and health status, along with recording of physical measures and the collection and storage of samples of plasma, serum, buffy coat, and washed red blood cells. Ten tissue slides are stored from the original tumor. All participants are contacted every 6 months for a health status assessment and medical records are reviewed for all reported cancer events, as well as deaths. All women who recur are encouraged to stay in the study with a flexible schedule for assessments to reduce participant burden. At year 4 of the study, complementary and alternative medicine services are assessed. At baseline, each group reported consuming approximately three vegetable servings/day. At 1 year the reported daily vegetable/vegetable juice servings were 7.1 for the intervention vs. 3.1 for the control and, for those who had been at least 2 years in the study, daily vegetable servings were at 6.4 intervention vs. 3.1 control. The maintained change in circulating carotenoids is: -carotene +89 percent intervention, 3 percent comparison; -carotene levels +57 percent intervention, 0 in comparison; and lutein +23 percent intervention and +7 percent in the comparison group. The study will use an intent-to-treat analysis to assess whether the study intervention effected outcomes for the overall study sample, as well as those under and over 55 years of age at randomization. For each analysis, four options will be identified: 1) the dietary pattern-reduced recurrence and mortality; 2) it reduced recurrence but not mortality; 3) it did not reduce recurrence but reduced mortality, and 4) it had no effect on either recurrence or mortality. The study will also investigate relationships between different components of the dietary pattern, circulating carotenoids, and study endpoints.

Cardiovascular Disease

▶ Title: *Genetics of Early-onset Stroke* NINDS
P.I.: Steven J. Kittner, M.D.
Institution: University of Maryland, School of Medicine
Department of Neurology, Baltimore
Grant No.: 1 R01 NS045012-01A1
Study Type: Clinical
Amount: $300,000

The long-term objective of this application is to characterize the genetic basis for ischemic stroke susceptibility in order to develop more effective prevention and treatment strategies. Current evidence suggests that the genes encoding the thrombomodulin-protein C and fibrinolysis systems are promising candidate stroke susceptibility genes because of their pivotal importance in thrombosis regulation and response to inflammation. The researchers postulate that: 1) novel genetic variants in the thrombomodulin, endothelial protein C receptor, and plasminogen activator inhibitor-1 genes predispose to the development of stroke, particularly infection-associated stroke, and 2) endothelial protein C receptor polymorphisms are associated with large vessel stroke, while thrombomodulin polymorphisms are associated with lacunar (small vessel) stroke. To obtain a sample size adequate to test these hypotheses, we propose a population-based, case-control study of ischemic stroke (1,033 cases and 1,064 controls) among young African American and Caucasian men and women. To complement an existing sample of female cases and controls, male cases (n = 600) will be recruited using a network of 59 hospitals in the Baltimore–Washington area. Age, gender, and race-matched controls (n = 600) will be recruited by random-digit dialing. A neurologist panel will perform stroke phenotyping. Historical risk factor data and blood samples for genetic studies will be obtained at a face-to-face interview. A comprehensive molecular analysis of the coding, promotor, and intronic regions of the three candidate genes will be performed to determine if sequence variation in these loci is associated with stroke. In addition to analyses of individual polymorphisms, intragenic haplotypes will be constructed and common haplotypes tested for association with stroke. Population substructure analysis will be used to identify and account for population stratification bias in the analyses. The proposed study will complement other associated studies of older stroke patients and will be a continuing resource for understanding the genetic basis of stroke risk.

▶ Title: *Altered Glucose and Lipid Metabolism In Obesity and Cardiovascular Disease* NHLBI
P.I.: Maureen J. Charron
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 1 R01 HL073163-01
Study Type: Basic
Amount: $200,000

This application proposes studies in mice to examine metabolic disturbances and cardiovascular disease (CVD) in animals that express only one functional copy of the insulin-stimulated GLUT4 transporter (a mouse model of type 2 diabetes), and hypothesizes that metabolic and cardiovascular changes may be mediated by altered expression of adipocyte-specific Acrp30 (adiponectin). The specific objectives of this proposal are: 1) to understand the molecular mechanisms underlying the metabolic changes that specifically affect male, but not female, GLUT4+/- mice or GLUT4+/- mice that overexpress GLUT4 in muscle; and 2) to test genetically

whether correction of Acrp30 downregulation in male GLUT4+/- will prevent or delay the onset of insulin resistance, visceral obesity, and/or CVD. Additionally, they will test whether complete lack of circulating Acrp30 in Acrp30-/-mice will provoke metabolic disturbance in female GLUT4+/- and exacerbate disease in male GLUT4+/- mice; 3) to assess the effects of high-fat, diet-induced changes in disease progression in GLUT4+/- compared to C57BL/6J mice; and 4) to determine transcriptional and translational changes in white adipose tissue (WAT) associated with visceral obesity and alterations following treatment with thiazolidinedione insulin sensitizers in hope of identifying novel therapeutic targets. Combined, this approach will provide a comprehensive systematic characterization of a mouse model of obesity-associated CVD derived from early impairment of insulin-mediated glucose flux into WAT, and directly address for the first time whether alterations in Acrp30 influence disease progression.

Craniofacial

▶ Title: *Brief Focused Treatment for TMD: Mechanisms of Action* NIDCR
P.I.: Mark D. Litt
Institution: University of Connecticut, School of Medicine, Farmington
Grant No.: 1 R01 DE014607-01A1
Study Type: Clinical
Amount: $100,000

TMD is a widespread chronic pain condition. Successful psychosocial treatments for TMD have been developed, but the mechanisms by which these treatments achieve their effects are not well known. The goal of this project is to evaluate the possible mechanisms responsible for treatment gains in TMD treatment. Men and women (N–106) with complaints of chronic facial pain for at least 3 months' duration will be recruited from the University Dental Clinics and from the community via advertisements and randomly assigned to either a Standard Conservative Treatment (STD) employing an intraoral splint plus anti-inflammatory agents, or to a Standard Treatment + Cognitive–Behavioral Treatment Program (STD+CBT), that will include standard treatment but also focus on changing self efficacy and decreasing catastrophization. Both treatments will entail six clinic visits. Dispositional and situational variables derived from a comprehensive model of pain coping will be measured before and after treatment. The situational variables, including coping responses, mood states, situational appraisals, and self efficacy, will be measured in an experience sampling paradigm four times daily using a handheld computer. This will be done to minimize retrospective biases that may have hampered earlier studies of treatment process. Dependent variables will be self-report measures of distress, pain, and interference with activities, as well as blood plasma levels of cortisol and selected cytokines, measured at the end of the 6-week treatment period, and at followup points thereafter up to a 12-month followup. It is expected that the STD+CBT treatment will result in measurable changes in constructs, such as self efficacy and catastrophization, and that these changes will be related to improved outcomes compared to the STD controls. It is also expected that outcome differences between groups will be associated with changes in inflammatory mediators (cytokine levels). Finally, it is suggested that changes in situational treatment process variables will be associated with changes in cytokine levels. The results may indicate the true active mechanisms of successful TMD treatment. If these mechanisms can be successfully identified, it would have important implications for the development of more effective treatment programs.

▶ Title: *Genotype and Temporomandibular Joint Disorders Vulnerability Types* NIDCR
P.I.: Christian S. Stohler
Institution: University of Michigan at Ann Arbor
Grant No.: 1 R01 DE 015396-01
Study Type: Basic and Clinical
Amount: $100,000

Temporomandibular joint disorders (TMJD) represent a major health problem and persistent TMJD pain is difficult to manage successfully. The majority of cases involve muscle. Laboratory evaluations proposed in this application permit new and critically important insight into the pathogenesis of persistent TMJD pain. The use of approaches from several different scientific disciplines, such as genetics, endocrinology, neurobiology of pain, and imaging of peripheral tissue, are proposed to probe and understand the system response of human subjects with respect to disease characteristics of TMJD and for which measurement opportunities in animals are limited. Based on supporting data, this research aims to provide new knowledge regarding the significance of a candidate gene that appears to exert a strong effect on critical hallmark features of persistent TMJD muscle pain. Because sensitivity to pain and inhibition of pain are traits of considerable variability, the effect of this gene on subject's response characteristics to experimentally induced jaw muscle pain will be studied. Furthermore, because women in their reproductive age make up the majority of patients treated with TMJD, the proposed research also focuses on whether estrogen significantly alters the system's response in subjects of a particular genotype.

▶ Title: *Neuronal Plasticity Related to Temporomandibular Joint Disorders and Fibromyalgia* NIDCR
P.I.: Dean A. Dessem
Institution: University of Maryland, Baltimore
Grant No.: 1 R01 DE 015386-01
Study Type: Basic
Amount: $100,000

The long-term objective of this project is to elucidate the role of craniofacial primary afferent neurons in musculoskeletal disorders such as temporomandibular disorders and fibromyalgia (FM) using animal models. Two hypotheses are proposed: Hypothesis 1: Masticatory muscle inflammation increases the number of trigeminal ganglion (TG) muscle afferent neurons that express substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin-1 receptor (NK-lr), and CGRP receptor (CGRPr). This increase involves a phenotypic switch in which muscle primary afferent neurons that do not normally express neuropeptides express SP, CGRP, NK-lr, and CGRPr following inflammation. It is proposed that this change contributes to muscle allodynia and hyperalgesia and can be modulated by pharmacologic manipulations thus providing insight into therapeutics for deep-tissue pain. This hypothesis will be tested by quantifying the distribution of TG muscle afferent somata and peripheral axons containing SP, CGRP, NK-lr, and CGRPr in three groups: i) control, ii) inflamed muscle, iii) inflamed muscle with intervention (anti-nerve growth factor, NK-lr, and CGRPr antagonists). This hypothesis will also be tested by determining the levels of CGRP, SP and gene expression for CGRP, SP within the TG using radioimmunoassay, and reverse transcriptase polymerase chain reaction. Hypothesis 2: SP and CGRP alter the functional properties of TG muscle afferent neurons in part by evoking spontaneous activity and increasing their excitability. It is predicted that substantially more group II, III, and IV TG muscle afferent neurons will be modulated by SP and CGRP following inflammation and that these functional alterations can be modulated pharmacologically. This hypothesis will be tested by characterizing the 1) spontaneous and evoked activity, and 2) active and passive membrane properties of TG muscle afferent neurons prior to muscle inflammation, following muscle inflammation, and following muscle inflammation combined with pharmacological intervention.

This will be achieved using intracellular electrophysiological recordings from masseter muscle afferent neurons in a trigeminal ganglion-masseter nerve *in vitro* preparation. Determination of soma size, axon diameter, and SP, CGRP immunoreactivity for physiologically characterized TG muscle afferent neurons will also test Hypothesis 1. Because a gender difference is reported for TMD and FM, both hypotheses will be tested in males, estrous females, and diestrous females.

▶ Title: *Estrogen Regulation of Inflammation Related to Temporomandibular Joint Disorders* NIDCR
P.I.: Phillip R. Kramer
Institution: Texas A&M University Health Science Center, College Station
Grant No.: 1 R01 DE015372-01
Study Type: Basic
Amount: $100,000

The long-range goal of this research is to identify and characterize genes through which steroidal hormones affect the onset and/or severity of human disease. The objective is to determine a gene in macrophages affected by estrogen withdrawal, as seen postpartum and at menopause, that functions in immune processes. The central hypothesis is that changes in estrogen concentrations directly regulate IgG Fc gamma receptor III-A (CD16a) expression resulting in a modulation of pro-inflammatory cytokine production and/or release from macrophages upon receptor binding. This hypothesis is based on recent findings *in vitro* that: 1) the level of Fc gamma RIIIA transcript increased in macrophage-like THP-1 cells and in primary, peripheral blood macrophages after estrogen removal; and 2) that the observed increase was dependent on transcription. The hypothesis also includes data from another lab that binding of Fc gamma RIIIA by anti-Fc gamma RIll monoclonal antibodies stimulates macrophage TNF-α and IL-1α release. Fc gamma RIIIA is a receptor that selectively binds IgG molecules, an important rheumatoid factor (RF) in autoimmune disease. Collectively, these data suggest that RF binding of this receptor stimulates cytokine release in rheumatoid arthritis and associated temporomandibular joint disorders (TMJD). To test the central hypothesis, Aim 1 will characterize macrophage cytokine production and release from stimulated macrophages after modulating Fc gamma RIIIA expression. TNF-α and IL-1α will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim 2 will focus on the mechanism inducing cytokine production and/or release upon Fc gamma RIIIA crosslinking. Signal transduction pathways and activated transcription factors will be identified, as well as regulatory TNF-α and IL-1α promoter sequences. Aim 3 will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ER α and/or ER β will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

▶ Title: *International Research Registry Network for Sjögren's Syndrome* NIDCR
P.I.: John Greenspan, Troy Daniels
Institution: University of California, San Francisco
Grant No.: N01 DE32636
Study Type: Clinical
Amount: $200,000

This contract will support the creation of an International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements will include: 1) to establish a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients; 2) to collect, process, store, ship, and analyze clinical information and biological specimens from patients and families with Sjögren's syndrome; and 3) to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome.

Diabetes

▶ Title: *Diabetes Prevention Program Outcomes Study* NIDDK
P.I.: Sarah Fowler, Ph.D.
Institution: George Washington University, Washington, DC
Grant No.: 5 U01 DK048489-09
Study Type: Clinical
Amount: $300,000

While the primary goal of the Diabetes Prevention Program (DPP) was to prevent the development of diabetes, an important secondary goal was to decrease the rate of cardiovascular disease and its risk factors. These clinically important outcomes were considered as secondary during the DPP due to a lack of sufficient power in the time allotted to the study to detect potential differences between the treatment groups (ongoing analyses of the DPP data suggest that there are significant differences between the groups with regard to some cardiovascular risk factors). Following the early conclusion of the DPP, the lifestyle and metformin arms were kept on their study interventions. Due to the marked effect of lifestyle in preventing or delaying type 2 diabetes, placebo and metformin participants were also offered the same lifestyle 16-session curriculum provided to the intensive lifestyle group during what was named the 'bridge period.' The DPP cohort being followed in the Diabetes Prevention Program Outcomes Study (DPPOS), is the largest study population with pre-diabetes, and the only population with type 2 diabetes studied from time of onset. The study cohort will provide insights regarding the clinical course of these metabolic disorders and will provide information on the persistence of the prevention or delay of type 2 diabetes. In addition, the DPP is the longest follow-up study of sustained weight loss ever conducted. Of major interest is the outcome of continued lifestyle and long-term weight loss, and metformin intervention in the gender-specific and minority subgroups during the DPPOS.

Gastroenterology

▶ Title: *Biofeedback for Fecal Incontinence and Constipation* NIDDK
P.I.: William E. Whitehead, Ph.D.
Institution: University of North Carolina, Chapel Hill
Grant No.: 3 R01 DK57048-03
Study Type: Clinical
Amount: $75,000

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

▶ Title: *Identification and Characterization of Stretch-dependent K+ Channels* NIDDK
P.I.: Sang D. Koh, M.D., Ph.D.
Institution: University of Nevada, School of Medicine, Reno
Grant No.: 1 R01 DK060687-01A2
Study Type: Basic
Amount: $175,000

The tunica muscularis of the gastrointestinal (GI) tract contains continuous sheets of smooth muscle cells. The diameters of GI organs change dramatically during digestion as food and chyme pass through the GI lumen. As a result of the distension and contractions that occur, individual myocytes experience dramatic changes in length, which may affect membrane potential, excitability, and responsiveness to agonist stimulation. Although many investigators believe that smooth muscles exhibit stretch-dependent contraction, stretch of colonic muscles does not initiate an obvious contractile response. Therefore, contraction does not appear to be a basic response to stretch in many GI organs. This may be a unique feature of GI smooth muscle that allows for volume expansion necessary for reservoir function. Thus, it is likely that cells of GI smooth muscles include ionic conductances that stabilize membrane potential and limit excitability during distension of the bowel wall. This may be an important aspect of the "myogenic response" to stretch that facilitates the reservoir function of regions of the GI tract and prevents interference in the coordination of segmental and/or peristaltic movement provided by the enteric nervous system. Such a mechanism likely involves stretch-dependent K+ (SDK) channels expressed by GI smooth muscle cells and interstitial cells of Cajal (ICC). If SDK channels are expressed in smooth muscle and ICC, they would provide a negative feedback pathway (stabilizing the membrane potential) by generating outward current in response to stretch. The following specific aims will be addressed: Aim 1) What is the distribution, biophysical, and pharmacological properties of SD channels in smooth muscle and ICC? Aim 2) What mechanisms modulate SDK channels? Aim 3) What is the physiological role of SDK channels in regulating membrane potential and excitability? Aim 4) What is the molecular species responsible for SDK channels in GI muscles? This study will demonstrate an important new class of channels in GI smooth muscles that may participate in the regulation of membrane potential and excitability and may mediate some of the response of these tissues to neurotransmitters.

▶ Title: *Improving Irritable Bowel Syndrome Outcomes* NINR
P.I.: Margaret M. Heitkemper, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 3 R01 NR04142-06S1
Study Type: Translational
Amount: $100,000

In the United States, it is estimated that 10 to 20 percent of the population experience symptoms compatible with a diagnosis of irritable bowel syndrome (IBS). IBS is a functional condition characterized by change in bowel patterns (e.g., constipation, diarrhea) interfering with functional activities and increasing health care utilization. Current recommended therapies include diet manipulation, self-management, psychotherapy, and motility and pain modulation via pharmacological therapy. The primary aim of this research is to compare the distribution of SERT polymorphisms across predominate bowel pattern subgroups and gender in people with IBS. It is hypothesized that the distribution of SERT polymorphisms (5′-flanking promoter region [5-HTTLPR] and in exon2 [VNTR]) will differ across predominate bowel pattern

subgroups and the distribution of SERT polymorphisms will differ by gender. Exploratory aims of this study include: 1) evaluate the relationships of SERT polymorphisms to symptom experiences and psychological profile; 2) test whether the degree of improvement in response to the CSM therapy differs by SERT polymorphism; and 3) evaluate the relationship of platelet-rich plasma 5-HT levels to SERT polymorphisms predominate bowel pattern. This study will provide information on the potential role of serotonin processing in IBS, as well as potential gender and bowel symptom predominance. Such results may ultimately be used to tailor therapies for this common health problem.

Genitourinary

▶ Title: *Regulation of Renal Xenobiotic Transport by Estrogens* NIDDK
P.I.: Carlotta Groves, D.V.M., Ph.D.
Institution: University of Arizona, Tucson
Grant No.: 1 R01 DK62097-1A1
Study Type: Basic
Amount: $186,345

Secretion of substrates from the blood into the urine by the renal proximal tubule plays an essential role for removal of potentially hazardous xenobiotics from the systemic circulation and out of the body. Many such xenobiotics are organic anion substrates and may, therefore, be cleared via interaction with the basolateral membrane organic anion transport (OAT) pathway. Recently, attention has been given to the study of cellular regulation of the OAT pathways, particularly OAT1- and OAT3-mediated transport. Knowledge of the regulation of OAT1 and OAT3 has much practical significance since factors that either suppress or prevent organic anion transport may increase exposure to dangerous xenobiotics to produce or at least exacerbate toxicity, whereas factors that stimulate organic anion secretion may be employed to enhance xenobiotic excretion to reduce environmental exposure. Studies have demonstrated that regulation by various hormonal systems modulates the expression and physiological function of various transport processes in the proximal tubule of the kidney. The sex steroid hormones testosterone and estrogen may serve to upregulate or downregulate, respectively, renal OAT and may account for sex-related differences in xenobiotic accumulation, excretion, and response to toxicity. The decrease in OAT associated with estrogen was reported in several studies to be related to an increased susceptibility to toxicity. In spite of the manifestation of gender-related differences in xenobiotic transport, little is understood about sex steroid hormone modulation of transport, particularly estrogens. Also, the presence of various endocrine-disrupting chemicals, environmental chemicals that possess sex steroid hormone, and particularly estrogenic activity (i.e., xenoestrogens) may, through their estrogenic effects, downregulate various transporters involved in renal accumulation and excretion of xenobiotics. To this end, the proposal will address the following overall objectives: 1) to characterize the effect of endogenous estrogen, 17b-estradiol, and the environmental xenoestrogens such as diethylstilbestrol (DES) and genistein on renal proximal tubule organic anion transport (OAT1 and OAT3); and 2) to determine the mechanisms by which these estrogens mediate their regulatory control of transport.

▶ Title: *Patient-centered Goals for Pelvic Floor Dysfunction* NICHD
P.I.: Kathie L. Hullfish, M.D.
Institution: University of Virginia, Charlottesville
Grant No.: 1 R03 HD42754-01A1
Study Type: Clinical
Amount: $74,000

Outcomes of pelvic floor dysfunction (PFD) treatments remain poorly measured, precluding scientific conclusions about their effectiveness. Currently available surgical and non-surgical therapies for these common conditions have not been rigorously scrutinized with regard to subsequent impact on individual quality of life or morbidity reduction. Although patient subjective opinions concerning surgical results are important, they are subject to interpretative difficulties. Several PFD-specific quality-of-life (QOL) scales have been developed and validated. These measures, however, do not assess the specific treatment goals of individual patients and, therefore, are limited when incorporating patient-centered goals into therapy. This prospective cohort study will classify and compare patient subjective goals and outcomes with respect to treatment interventions for disorders of the female pelvic floor. Preliminary investigation indicates an ample patient base for recruiting participants and feasibility of recruitment and followup. Four hundred and five patients with PFD will be enrolled and followed (270 in the conservative management arm and 135 in the surgical management arm). The primary outcome will be self-reported achievement of patient-derived goals. Data will be collected from patient interviews, questionnaires, physical examination, and laboratory testing. Patient-derived goals will be defined at baseline and followed over 12 months to determine the degree to which patient-derived goals are reported to have been met. Goal achievement among surgical patients will be compared to that among non-surgically managed patients. The study will provide the first estimates of goals and goal attainment in PFD, and determine whether goal attainment in surgically and non-surgically managed PFD is likely to differ. In addition, objective outcome measures and established QOL instruments will be compared and contrasted with the perception of goal achievement. While QOL measures allow consistent assessment of general PFD outcomes, assessing patient-centered goals allows individually tailored care of women with pelvic floor dysfunction. Patient goals, combined with clinical and QOL measures, may be used to provide comprehensive, multidisciplinary, patient-centered approaches to prevention, management, treatment, and rehabilitation.

▶ Title: *Weight Reduction for Incontinence Network (WIN)* NIDDK
P.I.: Deborah G. Grady, M.D.
Institution: University of California, San Francisco
Grant No.: 1 R01 DK064358-01
Study Type: Clinical
Amount: $250,000

Urinary incontinence is a common problem among women that causes distress, diminished quality of life, and dramatic limitations in daily functioning. Overweight women are at significantly increased risk of urinary incontinence; over 65 percent of women with incontinence are overweight. Data from short-term, preliminary studies suggest that weight reduction may significantly reduce incontinence episodes. Thus, weight loss may present a promising new approach to urinary incontinence, one likely to produce a cascade of broader health improvements in addition to reductions in frequency of urinary incontinence. Therefore, we propose to randomize 330 overweight and obese women with urinary incontinence (165 at each of two clinical centers) to a 6-month intensive behavioral weight control program or to usual care to determine the short-term effect of weight loss on frequency of incontinence and quality of life, to identify women most likely to benefit from weight loss, and to begin to explore the urodynamic mechanisms underlying incontinence improvement following weight loss.

HIV/AIDS

▶ Title: *Impact of Delivery Models in HIV Health Care* FIC
P.I.: Ximena L. Burbano, M.D.
Institution: Fundacion Santa, Bogota, Columbia
Grant No.: 1 R01 TW006218-01A1
Study Type: Clinical
Amount: $20,000

Colombia, which ranks fourth in the total number of HIV reported cases in Latin America, has designed different Delivery Health Care Models to provide coverage for HIV-infected patients. The proposed health research initiative, by a new foreign investigator, will evaluate for the first time, the utilization and cost implications of different representative delivery health care models in Bogota, Colombia. Assessment of cost effectiveness is vital not only in the area of treatment but also in regard to the use of diagnostics, provision of care, support services, and prevention strategies and programs. A multi-step evaluation of three main Delivery Health Care Models (Open Pre-Paid, EPS, Social Security) available in Bogota, will be undertaken. First, information will be obtained to determine the type of specific services available for each delivery model. Second, data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase, models will be compared in terms of health services utilization, costs, cost effectiveness, and which health care model best accomplishes delivery and sustains adherence to HAART. Evaluation of service utilization will consider the impact on disease progression, as indicated by CD4 cell count and viral burden. Outcomes will be aggregated to determine the level of total services required for adequate care for each delivery model. Findings from this project should provide necessary information to help determine the optimal use of HIV delivery services and help develop public health strategies to achieve equity in health services, for HIV-infected people in Colombia, and possibly other countries in Latin America.

▶ Title: *Interventions to Reduce HIV1 Incidence after Delivery* FIC
P.I.: James N. Kiarie, M.D.
Institution: University of Nairobi, Kenya, Africa
Grant No.: 1 R01 TW006640-01
Study Type: Clinical
Amount: $20,000

Women in sub-Saharan Africa face a high risk of HIV-1 acquisition during the first year postpartum which can be reduced by antenatal voluntary counseling and testing (VCT) and using female controlled HIV-1 prevention methods. In preventing heterosexual HIV-1 transmission, the success of female-controlled methods such as female condoms, the vaginal diaphragm, and vaginal microbicides depends on their use by women at a high risk of HIV-1 infection. In studies of prevention of mother-to-child transmission, little attention has been paid to women identified as HIV-1-negative and their risk of becoming infected after delivery. An understanding of the factors that influence HIV-1 incidence among uninfected mothers, and which female-controlled prevention methods are most acceptable to them, is crucial for preventing HIV-1 acquisition in these women, and hence, preventing additional mother-to-child transmission of HIV-1 in future pregnancies. This study proposes to determine the potential effectiveness of female-controlled HIV-1 prevention methods, and the impact of participation in perinatal HIV-1 prevention programs on HIV-1 incidence in the first year after delivery (assessed using a detuned ELISA at 9 to 12 months postpartum) in three sites in Kenya. The specific aims of the study are to: 1) determine the correlates of incident of HIV-1 infection among Kenyan women in the first year postpartum; 2) compare the incidence of HIV-1 infection among women who have participated in perinatal

HIV-1 prevention programs to the incidence among those who have not participated in these programs; 3) determine women's knowledge, attitudes, and willingness to use vaginal microbicides, the female diaphragm, and female condoms; and 4) estimate the effectiveness of the various HIV-1 prevention methods based on theoretical efficacy, the number and HIV-1 infection risk of women willing to utilize these methods. This study will provide important information on how to increase the effectiveness of female-controlled HIV-1 prevention methods by targeting women at a high risk of acquiring HIV-1 infection. The study will also identify ways to increase the impact of antenatal VCT in reducing HIV-1 incidence.

▶ Title: *Family Therapy Mechanisms in HIV-positive Women in Drug Recovery* NIDA
P.I.: Victoria Mitrani, Ph.D.
Institution: University of Miami, Coral Gables
Grant No.: 1 R01 DA016543-01A1
Study Type: Clinical
Amount: $335,609

This application proposes to investigate the family mechanisms by which Structural Ecosystems Therapy (SET) has its impact on HIV-positive women in drug recovery. This proposed study is a companion to NIDA Grant DA15004 (SETA Protocol), which investigates the efficacy of SET in a clinical trial with HIV-positive women who are in drug recovery. In the SETA Protocol, 176 women are randomly assigned to either SET or an HIV health group. The interventions last 4 months. SET works to transform the family system to reinforce sobriety, increase adherence with HIV medical care, and decrease sexual transmission risk behaviors in the target woman. The SETA Protocol only assesses the effect of SET on the recovering woman, not her family. Because SET targets changing the whole family as a means of helping the woman, we hypothesize that effects on the family as a whole (family functioning) and on individual family members will help to explain the woman's outcomes. The proposed study will enroll the women in the SETA Protocol and their families. A total of 538 family members are anticipated. Families are assessed at 4-month intervals for a period of 12 months. SET is hypothesized to affect family functioning (measured by self-report and observational methods). Changes in family functioning are hypothesized to affect the woman's drug abuse, HIV medication adherence, and HIV risk behaviors, as well as the individual functioning of her family members (psychological distress, drug use, and parent report of problem behaviors in children). The hypotheses will be tested using Latent Growth Curve Modeling. Understanding these mechanisms will facilitate the development of the next generation of family-based interventions for HIV-positive women in drug recovery.

▶ Title: *Drugs, Gender, and Healthcare Use Among HIV-positive Homeless* NIDA
P.I.: Elise Riley, Ph.D.
Institution: Regents of the University of California, San Francisco
Grant No.: 1 R01 DA015605-01A1
Study Type: Clinical
Amount: $200,000

This is a study of the impact of gender on health status and health care utilization among HIV-infected homeless individuals. The specific aims of the study are as follows: 1) to examine health care utilization in the cohort (i.e., primary care, drug treatment, and mental health services) and to determine differences in the patterns of health care utilization between HIV-infected marginally housed women and men at baseline and over a 3-year follow-up period; 2) to examine health outcomes in the cohort (physical and mental) and to determine the extent to which HIV-infected homeless women experience differences in health outcomes from men at baseline and over a 3-year follow-up period; and 3) to determine predisposing, enabling, and need factors influencing

the differences that women experience in health care utilization and health status. To achieve these specific aims, the following activities will be accomplished: 1) recruit an additional 49 women into the REACH cohort (the parent study) in order to increase statistical power for gender comparisons; 2) add detailed drug use, women's health, victimization, subsistence needs, and health care utilization variables to the existing REACH questionnaire; 3) implement a new SCID diagnostic assessment, in addition to the current REACH assessment, to thoroughly assess mental health; 4) employ the use of electronic health service databases to conduct new validity studies; and 5) conduct analyses specific to these new areas of interest. Achieving the proposed specific aims will only be possible with the addition of these new activities that will ultimately yield a new class of analyses. A detailed study of the impact and interactions of drug use, mental illness, health service use, competing needs like access to food, and health status will lead to a better understanding of ongoing mortality among HIV-infected marginally housed individuals, and create the foundation for more effective health interventions in a variety of settings.

▶ Title: *AIDS International Training and Research Program* FIC
P.I.: Arthur L. Reingold, M.D.
Institution: University of California, School of Public Health, Berkeley
Grant No.: 3 D43 TW000003-16S3
Study Type: Clinical
Amount: $50,000

The University of California, San Francisco–Gladstone Institute of Virology & Immunology Center for AIDS Research (UCSF-GIVI CFAR) will collaborate with the University of California, Berkeley's (UCB) Fogarty AIDS International Training and Research Program (AITRP) providing support for competitive training grants. Training grants will be led by CFAR members in collaboration with in-country collaborations in five resource-limited settings selected for the scale and stability of ongoing international HIV research. Training will focus on scientists from countries and projects integral to the UCB/UCSF AITRP. Training will be provided in country or in San Francisco and will take advantage of CFAR member expertise and CFAR Scientific Core capabilities. Training projects will be selected in a competitive mentored process after a publicly announced request for training proposals. Letters of intent responsive to the UCSF-GIVI focus on enhancing cross-disciplinary translational research will be invited to submit full, but brief, proposals linking training needs in-country with ongoing research projects. Proposals will be reviewed by an expert peer panel with final funding decisions made by the UCSF-GIVI CFAR co-directors. Effectiveness of training will be monitored and assessed by written progress reports and evidence of subsequent research grant funding and publications. To accomplish this goal, the following aims will be addressed: 1) evaluate the training needs at each of the five CFAR international sites; 2) support investigators from one or more priority sites in training at the UCSF-GIVI CFAR, and/or; 3) support UCSF-GIVI investigators to provide training at one or more priority sites(s); 4) provide access to UCSF-GIVI CFAR core laboratories and other resources for UCB/UCSF AITRP priority site investigators in pilot research projects; and 5) monitor and evaluate the success of research training support at priority sites as evidenced by important research grants, publications, and/or findings.

▶ Title: *Scale-up of Community-based HIV Prevention and Care* FIC
P.I.: Warren D. Johnson, M.D.
Institution: Well Medical College of Cornell University, Department of Medicine, New York, NY
Grant No.: 3 D43 TW000018-16S5
Study Type: Clinical
Amount: $50, 000

This proposal requests support for the Harvard University Program in Infectious Disease and Social Change/Partners in Health/Zanmi Lasante to continue training Haitian scientists in the performance of biomedical, epidemiological, and biosocial research in the programmatic implementation of HIV prevention and treatment and the care of individual patients with HIV in rural Haiti. The program is based at Clinique Bon Saveur in Change, Haiti, with responsibility for the provision of healthcare services for the population of the Central Plateau. The principal investigator is Paul Farmer, M.D., Ph.D., who is based at Harvard Medical School in the Program in Infectious Disease and Social Change. The training team has many years of experience in HIV prevention and treatment in rural Haiti, including the prevention of mother-to-child transmission, diagnosis, and treatment of TB and sexually transmitted disease, the prevention of opportunistic infections, and the use of highly active antiretroviral therapy. The principal investigator of the AITRP grant, Dr. Warren Johnson, is a long-standing supporter of the work done in Change and the Central Plateau, and this collaborative training program has been highly successful. The program will continue to emphasize long-term training and advanced research training in Haiti. Because HIV does not exist as a separate entity, the approach at PIH/ZL is to integrate the prevention and treatment of HIV with the most vulnerable and high prevalence groups that are seen at Clinique Bon Saveur. HIV-related services include: 1) HIV prevention and treatment, including expansion of access to voluntary counseling and testing (VCT); 2) the screening and treatment of STIs; 3) the prevention of mother-to-child transmission; and 4) TB case detection, treatment, and VCT (approximately 50 percent of HIV patients in the Central Plateau present with TB). These four activities are referred to by PIH/ZL as the "four pillars" of HIV control. The overall program goal of this grant is to provide training that will increase local capacity to perform research on service integration, diagnosis, and treatment of HIV in central Haiti within these four pillars of HIV control. Long-term benefits will include the increases in research capacity for future HIV-related research activities in Haiti.

▶ Title: *AIDS International Training and Research Program* FIC
P.I.: King K. Holmes, M.D., Ph.D.
Institution: University of Washington, College of Medicine, Seattle
Grant No.: 2 D43 TW000007-16
Study Type: Clinical
Amount: $50,000

This program proposes to develop a fifth AIDS International Training and Research Program (AITRP) site in New Delhi at the All India Institute of Medical Sciences (AIIMS) to address the growing HIV epidemic in India. Other target countries have been Kenya, Peru, Mozambique, and Thailand. The University of Washington (UW) AITRP selected AIIMS as the site for program expansion for several reasons. First, AIIMS is a premier institution for biomedical research and training in India, and successful collaborative research is already being performed between scientists at the UW (Uma Malhotra and Julie McElrath) and AIIMS (Pradeep Seth and Madhu Vajpayee) within the framework of an existing longitudinal cohort of HIV-1-infected subjects at AIIMS. Second, UW International Training and Research in Emerging Infectious Diseases (ITREID) has a site in New Delhi and the two programs will collaborate in their research and training efforts in the region. The IATRP program direction and the core/resource faculty will

be identical to that described for the parent program. The overall goal of this proposal is to develop a center for excellence in HIV-1 research in India with independent and sustainable research capacities in the prevention and control of HIV. A number of training needs and research priorities have been identified and include: 1) strengthening of the infrastructure for field research through training and capacity building in the area, 2) development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, and 3) strengthening the immunology research program through training of laboratory scientists in state-of-the-art immunology assays. The site will emphasize training in the Epidemiology Track and the Laboratory Track and will focus on long- and medium-term training. Recruitment of scientists into the Laboratory Track will occur in the Department of Microbiology. Recruitment efforts for trainees interested in the Epidemiology Track will take place in the Department of Community Medicine in collaboration with the Head of the AIDS Education and Training Program in New Delhi. Collaborative research and training during the first year will emphasize: 1) seroprevalence and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, 2) clinical profile of HIV-1 clade C infection in India, 3) cellular immunity to HIV-1 clade C viruses and diversity consideration in vaccine development, and 4) HIV-1 shedding and mucosal immunity. The existing longitudinal patient cohort will provide a foundation for new cohorts and continued collaborative research. Through these endeavors in multidisciplinary research and training, it is anticipated that the program will facilitate the establishment of critical expertise in biomedical and prevention research at the AIIMS to combat the growing HIV-1 epidemic in the region.

▶ Title: *HIV-1 Shedding from Female Genital Tract* NICHD
P.I.: Robert W. Coombs, M.D., Ph.D.
Institution: University of Washington, Seattle
Grant No.: 5 P01 HD040540-03
Study Type: Clinical
Amount: $253,187

Bacterial vaginosis (BV), the most common bacterial vaginal infection in women of reproductive ages, has been linked to the prevalence and incidence of HIV infection in women in cross-sectional and prospective studies. Women in sub-Saharan Africa have the highest prevalence of BV, approximately 40 to 50 percent in Uganda and Kenya. Prior research has demonstrated that while women can have their BV treated, recurrence rates are high due to poor male genital hygiene. The proposed research will test the hypothesis that poor genital hygiene in men represents an important risk factor for BV, and that improved male genital hygiene through application of an ethanol-based microbicides, especially in uncircumcised men will reduce the frequency of BV recurrence in women.

Immunity/Autoimmunity

▶ Title: *Sex-based Differences in Anti-viral Immunity and Systemic Lupus Erythematosus* NIAID
P.I.: Sally R. Sarawar, Ph.D.
Institution: LaJolla Institute, San Diego, CA
Grant No.: 1 R21 AI51862-01
Study Type: Basic
Amount: $50,000

Systemic lupus erythematosus (SLE) is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses, has been reported. However,

some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic loci that control disease susceptibility in these mice has been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci designated SLE 1, 2, and 3 have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gamma herpes virus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B-cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus with MHV-68, can induce or exacerbate autoimmune disease, and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection and whether their expression correlates with the induction of autoimmune disease.

▶ Title: *Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome* NIAMS
P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 1 R01 AR049772-01A1
Study Type: Clinical
Amount: $900,000

Thrombosis and pregnancy loss are common features of systemic lupus erythematosus (SLE), particularly in the presence of antiphospholipid (aPL) antibodies. The *in vivo* mechanisms by which aPL antibodies lead to vascular events and, specifically, to recurrent fetal loss are largely unknown. Our studies in a murine model of antiphospholipid antibody syndrome (APS) indicate that *in vivo* complement activation is necessary for fetal loss caused by aPL antibodies. This proposal represents a first-time effort to translate novel research observations on the potential role of complement activation in the pathogenesis of aPL antibody-mediated pregnancy loss to a clinically relevant human study. No study has investigated whether complement is activated in patients with aPL-associated poor pregnancy outcomes (with or without SLE), and whether particular patterns of complement activation characterize and thus can distinguish these patients from SLE patients without aPL antibodies or fetal loss, and from patients with normal pregnancy. Preliminary data in murine APS, the availability of more accurate tests of complement activation, and the recent development of effective and specific complement inhibitors argue persuasively that the role of complement in aPL-associated pregnancy complications should now be examined. Accordingly, the specific aim of the study is to determine whether elevations of split products generated by activation of the alternative or classical complement pathways predict poor fetal outcome in patients with antiphospholipid antibodies and/or SLE. The investigators propose a prospective observational study of over 400 pregnant patients, enrolled at six major clinical centers, and grouped and analyzed according to the presence or absence of aPL and pre-existing SLE. A core group of investigators with recognized expertise in SLE and aPL pregnancy, high-risk obstetrics, the basic biology of complement, and statistical methods in SLE studies have been assembled. Detailed medical and obstetrical information during the course of pregnancy and serial blood specimens for complement and cytokine assays will be obtained, and analyzed to identify predictors of poor fetal outcome. Placentas will be studied to characterize tissue pathology and

mediators of injury. RNA, DNA, serum, and urine will be stored for studies to elucidate temporal changes in gene expression during the course of complicated and uncomplicated pregnancies and to investigate genetic polymorphisms. The investigators hypothesize that this study will provide insights into the mechanisms of complement-mediated inflammatory disorders and suggest means to prevent, arrest, or modify these conditions. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable the investigators to initiate an interventional trial of complement inhibition in patients at risk for aPL antibody-associated fetal loss. The identification of such surrogate markers in aPL and SLE patients may also prove generally applicable to anticipate complications during pregnancy in disease-free women.

▶ Title: *Mechanism Regulating Neutrophil Activation in Pregnancy* NIAID
P.I.: Howard R. Petty, Ph.D.
Institution: Wayne State University, Detroit, MI
Grant No.: 1 R01 AI51789
Study Type: Translational
Amount: $50,000

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic, as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis), as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study offers a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

▶ Title: *Sex-based Differences in the Immune Response* NIAID
P.I.: Betty Diamond, M.D.
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 1 R01 AI51767-01
Study Type: Basic
Amount: $50,000

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and B cell activation, and to understand what underlies an estrogen-mediated breakdown in humoral self tolerance. The three Specific Aims are: Aim 1 investigates the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B-cell repertoire selection. Aim 2 addresses the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in Pyk-2-deficient mice. Aim 3 will characterize estradiol-induced signaling pathways that may alter B-cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of sexual dimorphism in this phenomenon.

▶ Title: *Brain Connections* NIAMS
P.I.: Michelle A. Petri, M.D.
Institution: John Hopkins University, Baltimore, MD
Grant No.: 1 R01 AR49125
Study Type: Clinical
Amount: $40,000

Neuropsychiatric manifestations of systemic lupus erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of co-morbidities or ethnicity/race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE from ten sites will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines, and adhesion molecules), and co-morbidities (race/ethnicity, depression, fibromyalgia, and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

▶ Title: *Identifying Genes for Neuropsychiatric Lupus* NIAMS
P.I.: Nilamadhab Mishra, M.D.
Institution: Wake Forest University, Winston-Salem, NC
Grant No.: 1 R21 AR49153
Study Type: Basic
Amount: $20,000

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of systemic lupus erythematosus (SLE) by microarray analysis. SLE is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity and mortality. It is a multisystem rheumatic disease with a wide variety of associated clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system function. Although the gene responsible for neurological disturbances in SLE is not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine gene expression in hippocampus and cerebellum are responsible for the neurological deficit.

▶ Title: *Antibodies to NR2 in Systemic Lupus Erythematosus* NIAMS
P.I.: Betty Diamond, M.D.
Institution: Yeshiva University, New York, NY
Grant No.: 1 R01 AR49126
Study Type: Clinical
Amount: $40,000

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with systemic lupus erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF), as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists and whether there is T-cell recognition of NR2 epitopes. Also, rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

▶ Title: *Brain Cell Death in MRL Mice: Targets and Mechanisms* NIAMS
P.I.: Boris Sakic, Ph.D.
Institution: McMaster University, Ontario, Canada
Grant No.: 1 R21 AR49163
Study Type: Basic
Amount: $100,000

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MRL-Ipr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, cerebrospinal fluid (CSF) neurotoxicity, and an anxiety/depressive behavioral state in MRL-Ipr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1) whether DNA fragmentation involves neurons, glial, and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining); 2) whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSIF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-Ipr mice); 3) whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology, with electron microscopy, by detecting DNA laddering with chemilumnescent method and caspase activation with immunohistochemistry); and 4) whether immunosuppression prevents neurodegeneration and CSF neurotoxicity.

▶ Title: *Virginia Mason/UCHSC Autoimmune Center* NIAID
P.I.: George S. Eisenbarth, M.D.
Institution: University of Colorado, Denver
Grant No.: 1 U19 AI50864-03
Study Type: Translational
Amount: $200,000

This grant consists of three research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in

genetic, immunologic, and environmental determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T-cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for rheumatoid arthritis and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. Project 3 will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

▶ Title: *T-Cell Reconstitution After Stem Cell Autograft* NIAID
P.I.: Jan Storek, M.D., Ph.D.
Institution: Fred Hutchinson Cancer Research Center, Seattle, WA
Grant No.: 5 R01 AI46108-04
Study Type: Clinical
Amount: $60,000

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

▶ Title: *How Does Blockage of CD40/CD40L Prevent Autoimmunity?* NIAID
P.I.: Matthias Von Herrath, M.D.
Institution: Scripps Research Institute, La Jolla, CA
Grant No.: 1 U19 AI51973-02
Study Type: Basic – Animal Models
Amount: $100,000

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

▶ Title: *Fine Specificity of Scleroderma Autoantibodies* NIAMS
P.I.: Judith James, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 1 R01 AR48045-02
Study Type: Translational
Amount: $200,000

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

▶ Title: *Studies of Collagen Gene Regulation in Two Murine Models* NIAMS
P.I.: Stephen H. Clark, Ph.D.
Institution: University of Connecticut, Farmington
Grant No.: 1 R01 AR48082-02
Study Type: Basic – Animal Models
Amount: $200,000

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

▶ Title: *EBNA-1 in Lupus* NIAID
P.I.: John B. Harley, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 2 R01 AI31584-09
Study Type: Basic
Amount: $200,000

The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. Novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus Nuclear Antigen-1(EBNA-1), which contains a peptide sequence that inhibits antigen presentation and class 1 HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-1 also contains sequences that appear to be differentially bound by SLE as opposed to normal sera. SLE will be studied from the perspectives of the anti-EBNA-1 humoral immune response, of EBNA-1 expression in B cells, and of EBNA-1 sequence variants.

▶ Title: *Registry and Repository of African Americans with Rheumatoid Arthritis* NIAMS
P.I.: Larry Moreland, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 1 N01 AR002247-000
Study Type: Clinical
Amount: $200,000

This 5-year project will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (RA), as well as a registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast United States will gather data, which will provide a resource for investigators interested in the genetics of RA in African Americans. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor-α [TNF-α]/lymphotoxin (LT)-α, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3 years disease duration in African Americans.

▶ Title: *Inflammation and Cardiovascular Disease in Rheumatoid Arthritis* NIAMS
P.I.: Joan Bathon, M.D.
Institution: Johns Hopkins University, Baltimore, MD
Grant No.: 1 R01 AR050026-01
Study Type: Clinical
Amount: $99,999

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in rheumatoid arthritis (RA). CVD-related deaths, congestive heart failure, and acute CV events are increased two- to fourfold in RA patients compared to matched controls, but the prevalence of conventional risk factors for CVD is not increased. This suggests that the disease itself, presumably via chronic inflammation, is an important risk factor for accelerated CVD. Our hypothesis is that RA constitutes an independent risk factor for accelerated CVD. The investigators hypothesize that inflammation due to RA promotes and exacerbates CVD, independent of conventional CV risk factors. This proposal is an ancillary proposal to the Multi-Ethnic Study of Atherosclerosis (MESA), a unique prospective multicenter study to identify risk factors for incident and progressive subclinical and clinical CVD in the general population. Two hundred RA patients followed in the Johns Hopkins Arthritis Center will be recruited and will be compared to the prevalence and progression of subclinical CVD in this population to the 1,066 MESA participants, who are not RA patients, from the Hopkins Field Center. The degree to which inflammation contributes to increased CVD in RA patients will be examined, after adjusting for conventional CVD risk factors. Specific aims are as follows: 1) In a cross-sectional analysis, the distributions of a measure of atherosclerosis (coronary calcium by computed tomography) and measures of left ventricular (LV) structure and function (by magnetic resonance imaging) between RA patients and controls will be assessed and compared; whether differences between the groups in coronary calcium and LV dysfunction are explained by markers of inflammation in RA. 2) In a prospective analysis, the changes in coronary calcium over 3 years between RA patients and controls will be compared. The degree to which elevated markers of inflammation contribute to differences in progression of coronary calcium will be determined. 3) The associations of various markers of inflammation and disease activity/severity, as well as conventional CVD risk factors, with coronary calcium and LV dysfunction at baseline and over 3 years, among RA patients will be assessed. Particularly, the potential dose-response relationships of various markers of inflammation and disease activity/severity to coronary calcium and LV dysfunction will be examined. RA is a chronic inflammatory disease that can be considered to be a model of accelerated CV disease. Lessons learned from the study of CVD in RA may promote the fundamental understanding of inflammatory mechanisms of CVD.

▶ Title: *UCSF Autoimmunity Center of Excellence* NIAID
P.I.: David Wofsy, M.D.
Institution: University of California, San Francisco
Grant No.: 1 U19 AI056388-01
Study Type: Clinical
Amount: $60,000

The broad aim of this application is to translate advances in immunology and molecular biology into practical, safe, and effective therapies for people with autoimmune diseases. Toward this end, the investigators will participate in collaborative clinical trials of novel immunotherapies, and we will conduct basic research into the mechanisms that lead to autoimmunity, as well as the mechanisms that can be harnessed to prevent autoimmunity. This proposal to become an Autoimmunity Center of Excellence consists of a Clinical Center, two basic research projects, and an Immune Function Monitoring Core. Investigators involved in the Clinical Center application have extensive experience in the conduct of clinical trials in diverse autoimmune diseases. This application focuses primarily on systemic lupus erythematosus, multiple sclerosis, and type I

diabetes mellitus. Two clinical protocols are proposed, both based on basic research conducted at UCSF by participants in this proposal. Protocol 1 is based on the observation that blockade of T cell co-stimulation by CTLA4Ig, in combination with conventional therapy with cyclophosphamide, produces long-lasting benefit in murine lupus. It tests the hypothesis that this approach to therapy will be effective in people with lupus nephritis. Protocol 2 is based on the observation that HMG-CoA inhibitors (statins) retard murine models for MS. It tests the hypothesis that atorvastatin will prevent progression to MS in patients at high risk.

▶ Title: *Treatment of Autoimmune Disease by Cost Co-stimulatory Signal* NIAID
P.I.: Samia J. Khoury, M.D.
Institution: Brigham and Women's Hospital, Boston, MA
Grant No.: 2 U19 AI046130-05
Study Type: Clinical
Amount: $60,000

There have been tremendous advances in the field of autoimmunity in the last 20 years, and our understanding of the mechanisms underlying autoimmune disease has grown exponentially. True tolerance is likely to arise not from improved immunosuppression, but from improved understanding of the normal mechanisms that generate and maintain self-tolerance, and the ability to manipulate these mechanisms for the prevention and treatment of autoimmune diseases. The mechanisms of autoimmunity that underlie many diseases are similar, and an integrated multi-specialty approach for evaluating new and emerging therapies would provide the opportunity to integrate knowledge from the various specialties.

▶ Title: *Suppression and Exacerbation of B- and T-cell Responses* NIAID
P.I.: Ignacio Sanz, M.D.
Institution: University of Rochester, NY
Grant No.: 1 U19 AI056390-01
Study Type: Clinical
Amount: $60,000

The overarching goal of this proposal is to establish an Autoimmunity Center of Excellence at the University of Rochester. This goal is based upon our belief that the understanding of human autoimmunity requires the concerted effort of basic and clinical scientists working together in an intellectual framework that provides constant feedback between bench studies and therapeutic interventions. Our center will concentrate on studies relevant to the pathogenesis and treatment of type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), and systemic lupus erythematosus (SLE). Both types of studies are based on the unifying idea that abnormalities of B- and T-cell function are at the core of these autoimmune diseases. Basic Project 1 will investigate the role of regulatory T cells (Treg) in the pathogenesis of T1DM and will generate new re-agents that will allow investigators to more specifically identify human Treg cells. Basic Project 2 will elucidate the role of IL-12p40 monokines in MS and determine whether defects in Treg function exist in patients with this disease. Basic Project 3 will study B-cell homeostasis and the cellular origin of disease-specific autoantibodies in SLE. In addition, this project will investigate whether abnormal Treg function contributes to the activation of autoimmune B cells and T cells in SLE. These pathogenic mechanisms will serve as the theoretical basis for our clinical trials. Clinical Project 1 will study the clinical and immunological consequences of B cell depletion in SLE using the anti-CD20 monoclonal antibody, Rituximab. Clinical Project 2 will test the clinical and immunological effects of anti-IL-12 in patients with MS. We expect that the studies proposed will result in information that will not only improve our understanding of the disease in question but will also suggest new avenues of research for the other autoimmune diseases targeted by our center.

▶ Title: *Modulation of B-cell Responses in Autoimmunity* NIAID
P.I.: Eugene W. St. Clair, M.D.
Institution: Duke University, Durham, NC
Grant No.: 1 U19 AI056363-01
Study Type: Clinical
Amount: $60,000

The proposed center will focus on the modulation of B-cell responses in autoimmunity. In autoimmunity, B cells not only serve as the source of pathogenic autoantibodies, but they also may function as antigen-presenting cells (APCs) and stimulate pathologic inflammation through a variety of mechanisms. B-cell function is regulated via the B-cell receptor complex, as well as other B-cell-specific cell surface ZAI1 CL-I (M2) 3 1 U19 AI056363-01 ST CLAIR, E antigens, including CD20 and CD22. Growing evidence, including our results, indicates CD20 and CD22 are attractive targets for immunotherapy of autoimmune diseases. In addition, the investigators have shown inflammatory stimuli, such as tumor necrosis factor (TNF), can promote the emigration of B-cells from the bone marrow, transferring large numbers of developing B lymphocytes to the periphery. We hypothesize aberrantly activated B-cells are pivotal to the clinical expression of autoimmunity, and the resulting inflammatory state affords an environment for abnormal development of autoreactive B-cells and further dysregulation of the immunological response. Two interrelated basic research projects are proposed to investigate this hypothesis. Dr. Thomas Tedder, Professor and Chair of Immunology, will direct a project examining the roles of CD20 and CD22 in the regulation of B-cell function in mouse, taking advantage of a unique panel of CD20- and CD22-directed monoclonal antibodies developed in his laboratory. The other project will be headed by Dr. Garnett Kelsoe, Professor of Immunology, and will investigate to what extent inflammatory stimuli, such as TNF, influence the trafficking of immature B-cells and selection of the autoreactive B-cell repertoire. A clinical component led by Dr. St. Clair and other experienced physician-scientists will complement the basic research projects. This group has expertise in rheumatoid arthritis (RA), systemic lupus erythematosus, pemphigus vulgaris (PV), and other autoimmune diseases, as well as access to many different patient populations for clinical studies. One of the proposed trials will evaluate the safety and clinical efficacy of anti-CD22 monoclonal antibody therapy for RA, while the other will investigate infliximab (anti-TNF) therapy for PV. Each of the trials includes mechanistic studies that are integrated with the goals of the basic research projects, providing synergy within the center. An administrative core will oversee the management of these projects. Overall, the proposed center will efficiently bridge basic and clinical investigations and should produce new insights into the immunotherapy of autoimmune disease.

▶ Title: *University of Alabama at Birmingham Autoimmunity Center for Excellence* NIAID
P.I.: Robert H. Carter, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 1 U19 AI056542-01
Study Type: Clinical
Amount: $60,000

The University of Alabama at Birmingham (UAB) has an outstanding record in basic immunology and in testing of novel, translational therapies for autoimmune diseases. The UAB Autoimmunity Center of Excellence (ACE) is a multidisciplinary, collaborative program to unite these strengths to accelerate the development and testing of translational therapies for autoimmune disease. To accomplish this, the UAB ACE will promote basic and translational research and sponsor clinical trials of novel immunomodulatory agents. As part of this mission, the UAB ACE will foster communication between basic and clinical investigators and between those focused on different immune-mediated diseases at UAB and nationally.

▶ Title: *Autoimmunity Centers of Excellence* NIAID
P.I.: Betty Diamond, M.D.
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 1 U19 A1056362-01
Study Type: Clinical
Amount: $278,506

The Autoimmunity Center of Excellence at the Albert Einstein College of Medicine will encompass research projects, an infrastructure for clinical trials and an administrative core. This center reflects an interdisciplinary approach to autoimmune disease. It involves a collaboration of clinicians and basic scientists that is focused on translational studies to develop new therapeutic strategies. The research component includes three research projects. Each project has the goal of developing new targets for therapy in autoimmune disease. The first project is a study of the effects of statins alone or in conjunction with CTLA-4Ig in the NZB/W mouse model of lupus. This project will include a study of the effect of statins on peripheral blood mononuclear cells of lupus patients. The second project is a study of the effect of CD22 overexpression on B cell development and on autoantibody production in murine models of SLE and includes a study of a CD22 polymorphism reported to associate with lupus. Overall it will explore whether inhibition of CD22 represents a useful therapeutic strategy. The third project is a biophysical study of the polymorphism of murine 2 microglobulin that is required for the expression of diabetes in NOD mice. This study will provide a comprehensive biophysical characterization of the features of TCR/MHC-peptide complexes that are directly relevant to eliciting diabetes. These studies promise to provide the atomic and molecular mechanisms responsible for disease development and thus may lead to novel strategies for the design of therapeutics that will limit disease-associated T-cell reactivity. The clinical infrastructure is capable of performing clinical trials in autoimmune rheumatic diseases, type 1 diabetes, autoimmune hematologic diseases, and inflammatory bowel disease. In addition, there are proposals for a clinical trial of DNase I in serologically active, clinically inactive lupus and for a trial of statin therapy as a steroid sparing agent in rheumatoid arthritis. Finally, the center will include an administrative core for coordination and implementation of center activities.

▶ Title: *An Animal Model for Graves' Disease/Ophthalmology* NEI
P.I.: Juan C. Jaume, M.D.
Institution: UCSF/ VAMC, Department of Medicine, San Francisco, CA
Grant No.: 1 R03 EY014962-01
Study Type: Basic
Amount: $126,000

The ophthalmopathy of Graves' disease is a disfiguring, sight-threatening condition of unclear pathogenesis and not specific of definitive therapy. Graves' disease primarily manifests with hyperthyroidism that results from the stimulation of the TSHR by specific autoantibodies that mimic the effect of TSH. Often the ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves' disease exists. Recently, an animal model has been developed in which a proportion of individuals manifest immunological and endocrinological features of Graves' disease.

Infectious Diseases

▶ Title: *A Prospective Study of Chronic Fatigue Syndrome in Adolescents* NIAID
P.I.: Renee R. Taylor, Ph.D., M.A.
Institution: University of Illinois at Chicago
Grant No.: 1 R01 HD043301-01A1
Study Type: Clinical
Amount: $300,000

This project will prospectively study the relationship between infection with mononucleosis and the onset and course of chronic fatigue syndrome (CFS) over time in adolescents. The following hypotheses will be tested using a prospective, case-control design: 1) Baseline predictors of post-infectious CFS and fatigue severity at 6 months will include greater levels of baseline psychological distress, having a psychiatric diagnosis at baseline, a greater degree of stressful life events at baseline, and higher levels of activity prior to initial infection; 2) Adolescents with CFS, compared with matched controls, will report higher levels of psychological distress, higher rates of psychiatric diagnoses, a greater degree of stressful life events, and lower levels of physical activity following infection at the 6-, 12-, and 24-month time points; and 3) Compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol (peak and trough), reduced natural killer cell function and count, and elevated proinflammatory cytokines at the 6-, 12-, and 24-month time points. At the 6-month time point (clinic visit), adolescents with CFS will also demonstrate higher rates of orthostatic intolerance; and 4) In response to an exercise challenge test at the 6-month time point, compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol and plasma ACTH, and elevated cytokines—illustrating impaired communication between neuroendocrine and immune systems with physical stress. An exploration of the nature and timing of these relationships would provide a preliminary model of etiology and natural course of illness for adolescents with post-viral CFS. Results from this investigation may assist physicians in identifying adolescents at high risk for CFS and allow them to initiate preventative measures.

▶ Title: *Sex in Viral Myocarditis* NIAID
P.I.: Sally A. Huber, Ph.D.
Institution: University of Vermont, Burlington
Grant No.: 1 R21 AI51850
Study Type: Translational
Amount: $50,000

Myocarditis is an inflammatory disease of the myocardium. Approximately 65 percent of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes, while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN) gamma and female cells producing interleukin-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

▶ Title: *Seroprevalence/Incidence of Genital Herpes* FIC
P.I.: Edith Nakku-Joloba
Institution: New Mulago Hospital, Uganda, Africa
Grant No.: 1 R01 TW006672-01
Study Type: Public health clinical
Amount: $20,000

Prevalence of herpes simplex type 1 and 2 virus (HSV-1 and -2) infection is high worldwide and is highest in developing countries like Uganda. International and local health organizations have called for studies to characterize genital herpes epidemiology in sub-Saharan Africa. Population estimates are needed for policy, for planning interventions, for valid measures of the effect of interventions, and for research on new therapies and potential vaccines. The overall goal of this study is to determine the burden of infection and assess the modifiable risk factors associated with HSV-1 and -2 infection in Kampala, Uganda, with an aim of prevention of spread and relief of those who suffer with genital herpes. The proposed study will aim: 1) to estimate the age- and sex-specific prevalence of HSV-1 and -2; 2) to estimate the incidence of HSV-1 and -2 in an inception cohort of HSV-2 negative persons in an urban population in Uganda; and 3) to identify modifiable risk factors associated with HSV-1 and -2 prevalence and incidence in this population. The proposed study will be a two-stage stratified random population sample survey of female and male participants, 15 to 65 years old, in Kawempe division of Kampala District. To estimate prevalence of HSV-1 and -2, a cross-sectional serological survey at baseline will be done using type-specific ELISA tests for HSV-1 and -2. Incidence will be assessed in an inception cohort of HSV-2-negative persons by six monthly testing for HSV-2. Risk factors for genital herpes will be assessed using a standardized questionnaire to collect information on age; sociodemographic characteristics; sexual behavior; sexual partner characteristics, such as age differentials; and HIV-infection status. Incidence densities and relative risks will be calculated from new HSV-2 infection and risk factors that predispose to HSV-2 incidence (such as age, sex [gender], sexual behavior); and HIV infection analyzed in a Cox proportional hazards model. By conducting a population study in an urban area in a country where rural studies show high prevalence, we will describe the epidemiology genital herpes, gaining new knowledge about genital herpes in urban Uganda and highlighting the modifiable risk factors which can be targeted for effective interventions.

Menopause

▶ Title: *Study of Women's Health Across the Nation II (SWAN II)* NIA
P.I.: Karen Mathews, Ph.D., Coordinating Center (University of Pittsburgh), and multiple sites (UCLA, University of Michigan, University of California–Davis, Mass General, Rush–Presbyterian–St. Luke's Medical Center, UMDNJ, and University of Pittsburgh)
Institutions: New England Research Institute, Watertown, MA
Grant No.: 5 U01 AG12546-10
Study Type: Clinical
Amount: $250,000

SWAN consists of both cross-sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology/physiology of premenopause. Five ethnic groups are included: Caucasian, African American, Hispanic, Chinese, and Japanese. There are seven sites across the country: Boston, Pittsburgh, Chicago, Michigan, UCLA, UC–Davis, and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled, ranging in age from

40 to 55 years, to determine the age of menopause. The longitudinal study has approximately 3,150 women (450 at each site), between the ages of 42 to 52, to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone binding globulin [SHBG]), and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

▶ Title: *The Study of Women's Health Across the Nation (SWAN II) Sub/Pilot Projects* NIA
P.I.: Gail Greendale, M.D., and Kim Sutton-Tyrrell, Ph.D.
Institution: University of California, Los Angeles, and
University of Pittsburgh, PA
Grant No.: 3 U01 AG012539-10S2
Study Type: Clinical
Amount: $202,756

The proposed research is comprised of three analyses, which would use data collected under the aims and protocols of the most recent SWAN renewal application. These data will form the basis of a pilot study with analyses to determine the characteristics of those subsets of women selecting hormone therapy, discontinuing therapy, and their experience regarding the emergence (or re-emergence) of symptoms and accelerated bone loss. These themes have been chosen because in the wake of the WHI findings, the NIH and physicians worldwide have been besieged by calls and correspondence from women who were distressed about having to relinquish Menopause hormone therapy (MHT), experiencing symptoms and left in the dark about how these problems might resolve. Since SWAN is a natural history study in a multiethnic population, it will be very valuable in generating preliminary data to begin addressing some of these issues (e.g., why women selected MHT, the impact of the WHI findings on their short- and long-term choices and behavior, and/or indicating where more research is needed). Preliminary findings from these analyses can serve as the basis for hypothesis-driven, investigator-initiated studies in this area.

▶ Title: *Menopausal Depression: Chronobiologic Basis* NIMH
P.I.: Barbara L. Parry, M.D.
Institution: University of California–San Diego, La Jolla
Grant No.: 5 R01 MH059919-03
Study Type: Clinical
Amount: $100,000

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

▶ Title: *Centers for Dietary Supplements Research: Botanicals* NCCAM
P.I.: Norman Farnsworth, Ph.D.
Institution: University of Illinois at Chicago
Grant No.: 5 P50 AT00155-04
Study Type: Clinical, basic
Amount: $100,000

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

▶ Title: *Phytoestrogens and Progression of Atherosclerosis* NCCAM
P.I.: Howard N. Hodis, M.D.
Institution: University of Southern California, Department of Medicine, Los Angeles
Grant No.: 5 U01 AT001653-02
Study Type: Clinical
Amount: $200,000

The fear and discontent with traditional hormone replacement therapy (HRT), coupled with the interest in natural products, has resulted in an increased use of soy protein as a postmenopausal therapeutic alternative by both women and their physicians alike. Evidence from epidemiological and non-humane primate studies indicate that isoflavone-rich soy protein has antiatherogenic activity, evidence supported by a large body of data that indicate mechanistic and biologic plausibility. No studies to knowledge have been published or proposed to determine the long-term effects of soy protein on the progression of atherosclerosis in postmenopausal women. The investigators propose to conduct a 2.5 year, randomized, double-blind, placebo-controlled trial of isoflavone-rich soy protein in 300 healthy postmenopausal women without clinical evidence of cardiovascular disease. They hypothesize that relative to placebo, isoflavone-rich soy protein (supplying genistein, daidzein, and glycitein) will reduce the progression of subclinical atherosclerosis in healthy postmenopausal women. The primary end point will be the progression of subclinical atherosclerosis measured as the rate of change in common carotid artery intima-media thickness in computer image processed B-mode ultrasonograms, a well-established non-invasive arterial imaging end point for antiatherosclerosis trials, Isoflavone-rich soy protein may provide a safe and effective alternative approach for extending premenopausal ardioprotection afforded by endogenous estrogen into menopause without the increased risk of thromboembolic events and certain cancers associated with traditional HRT. Since many postmenopausal women are using spy products to maintain their health, it is important to understand whether soy protein has an antiatherogenic effect so that women can make a truly informed decision concerning their expectations of this form of postmenopausal therapy. The question as to whether soy protein is effective in reducing progression of atherosclerosis in postmenopausal women is not only timely, but also of immense medical and financial importance since atherosclerosis remains the number one killer of postmenopausal women.

▶ Title: *Baseline Measurements for Effects of Soy on Bone, Cancer, and Cognition Health* NCCAM
P.I.: Howard N. Hodis, M.D.
Institution: University of Southern California, Department of Medicine, Los Angeles
Grant No.: 3 U01 AT001653-02
Study Type: Clinical
Amount: $48,000

The parent application, entitled Phytoestrogens and the Progression of Atherosclerosis, is a 5-year study (2.5-year, randomized, double-blind, placebo-controlled clinical trial) to test the hypothesis that diet supplementation with isoflavone-rich soy protein is antiatherogenic due to the estrogen agonist effects of soy isoflavones. The study seeks to resolve the question as to whether soy phytoestrogens are effective in reducing the progression of atherosclerosis in postmenopausal women. Since the effects of soy phytoestrogens presumably extends beyond the benefits to cardiovascular diseases to bone health, cancer prevention, and cognition and vasomotor improvement, additional tests to test the effects of soy on bone, cancer, and cognition would yield tremendous information with little additional investment. The baseline measurements that will be obtained at the initial examination will include DEXA for bone density, mammogram, and cognition tests.

Mental Health

▶ Title: *Health Survey of Two-Spirited Native Americans* NIMH
P.I.: Karina L. Walters, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 1 R01 MH65871-01
Study Type: Clinical
Amount: $175,000

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the United States. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to: 1) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); 2) test the direct associations between trauma and health outcomes; 3) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and 4) examine the mediating role of substance use on the trauma-HIV sexual risk behavior and trauma-mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

▶ Title: *Stress Response Differences in Females: Estradiol's Role* NIMH
P.I.: Martha M. Faraday, Ph.D.
Institution: The Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, MD
Grant No.: 1 R03 MH065945-01
Study Type: Basic
Amount: $74,350

In response to stress, premenopausal women are more likely to become depressed than are men, suggesting that being female and exposure to cycling female sex hormones may constitute part of depression vulnerability. Only some women develop depressive illness, however, indicating that women differ in stress sensitivity and depression vulnerability. Rodent models of depression that examine responses of stress-vulnerable vs. stress-resistant females would be valuable to understand the biologic basis of differential stress and depression vulnerability in women, but models of depression generally have used male rats as subjects. Preliminary data indicate that Sprague-Dawley female rats are markedly more sensitive to stress than are Long-Evans female rats across several behaviors and biologic indices, including a behavioral model of depression and hypothalamo-pituitary-adrenocortical (HPA) axis responses. These differences in response to stress could be the result of many factors, including actions of estradiol on brains that are different and line differences in how stress affects estradiol levels or estrus cycling. Estradiol is the major sex hormone with behavioral and biologic actions in females. Estradiol interacts with stress-sensitive brain systems (i.e., serotonergic, dopaminergic) that control the behaviors under study. Estradiol also interacts with the HPA axis. Therefore, examining estradiol's role in stress responding of stress-sensitive female rats (Sprague-Dawley) and stress-resistant female rats (Long-Evan) is a critical step toward understanding why some females are more vulnerable to stress and depression than others. Behavioral and corticosterone responses of Sprague-Dawley and Long-Evans females that are intact, ovariectomized, or ovariectomized with estradiol replacement will be evaluated in response to daily restraint stress. Responses also will be compared with intact male rats. To determine whether female line differences in response to stress are the result of changes in estrus cycling or line differences in estradiol levels, estrus cycle, and estradiol levels of intact females also will be assessed.

▶ Title: *CARE Intervention for Depressed Mothers and Their infants* NINR
P.I.: June A. Horowitz, Ph.D., R.N.
Institution: Boston College, Chesnut Hill, MA
Grant No.: 1 R01 NR08033-01A1
Study Type: Clinical
Amount: $100,000

Postpartum depression (PPD), a commonly experienced childbirth complication, jeopardizes mothers' ability to interact responsively with their infants. Onset during the critical period of the first few months of infants' lives threatens the maternal-infant relationship and adversely affects infant development. Despite the clinical significance of the problem, there is limited information on the treatment of maternal-infant relational disturbances associated with PPD. The overall goal of this randomized clinical trial is to mitigate negative effects of PPD on infants' development by promoting responsive interaction between depressed mothers and their infants. The specific aim is to test the efficacy of the relationship-focused CARE (Communicating and Relating Effectively) intervention in increasing maternal-infant relational effectiveness, increasing infant clarity of cues and responsiveness to parent, and reducing parenting stress for the treatment group at 3-, 6-, and 9-months after delivery. This proposed study builds on preliminary studies that: 1) demonstrated the feasibility of screening women for postpartum depression, and 2) tested the efficacy of a

behavioral coaching intervention delivered by nurses to promote maternal-infant responsiveness between depressed mothers and their infants. In this study, the intervention coaching is adapted to problematic maternal interactive behaviors that are associated specifically with PPD. Nurses will screen approximately 1,500 postpartum women for PPD, randomly assign a minimum of 116 eligible participants to either the treatment or control group, and confirm depression status with a diagnostic interview. Using a repeated measures design, data will be collected at 1, 3, 6, and 9 months postpartum. Standardized instruments will evaluate depression symptoms and parenting stress; blind coding of videotaped maternal-infant interaction will measure maternal-infant relational effectiveness and infant behavioral responses. The CARE intervention will be conducted during home visits at 1, 2, 3, 4, and 6 months postpartum by teaching mothers to interpret their infants' behavioral cues and to respond effectively. R-MANOVA will be used to test the study hypothesis and to answer the research questions. Outcomes are expected to contribute to knowledge of evidence-based nursing practice models for the treatment of maternal-infant relational problems associated with PPD.

Musculoskeletal Systems

▶ Title: *Osteoarthritis Initiative* NIAMS
Study Type: Clinical
Amount: $800,000

The Osteoarthritis Initiative (OAI) is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis (OA), a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5 to 7 years, the OAI will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

▶ Title: *Glucocorticoids Alter the Birth and Death of Osteoblasts* NIAMS
P.I.: Robert Weinstein, Ph.D.
Institution: University of Arkansas for Medical Sciences, Little Rock
Grant No.: 5 R01 AR46191-04
Study Type: Clinical and basic
Amount: $100,000

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

▶ Title: *Low-dose Doxycycline Effects on Osteopenic Bone Loss* NIDCR
P.I.: Jeffrey B. Payne, D.D.S.
Institution: University of Nebraska, Lincoln
Grant No.: 1 R01 DE12872-02
Study Type: Translational, clinical
Amount: $324,398

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

▶ Title: *Factors Affecting the Bone Response and Non-Response* NIAMS
P.I.: Laura A. Milliken, Ph.D.
Institution: University of Massachusetts, Boston
Grant No.: 1 R03 AR047932-01 A1
Study Type: Clinical
Amount: $99,999

The effects of exercise and hormone replacement therapy (HRT) on bone mineral density (BMD) have been investigated by many researchers in a wide variety of subject populations. However, there are relatively few studies on postmenopausal women involving substantial sample sizes that have examined the BMD response to longer-term exercise therapies (≥ one year). It has been suggested that any therapy that functions to decrease bone remodeling will initially increase BMD solely as a consequence of the bone remodeling transient. This transient is simply the completion of remodeling packets (formation and mineralization) that were activated prior to the administration of the treatment. Therefore, the true effectiveness of the therapy should be evaluated after this transient has passed. This underscores the need for longer-term studies of exercise, HRT, or any therapy thought to prevent bone loss. Additionally, despite the general notion that exercise and/or HRT can prevent bone loss, there remains a large number of postmenopausal women who do not respond to the prescribed treatment. Conversely, some women respond much more than would have been predicted based on our current body of knowledge. The aims of this study are to: 1) develop statistical models to predict 1- through 4-year changes in regional and total body BMD from nutritional, hormonal, biochemical, body composition, physical activity, and psychosocial variables in post-menopausal women; and 2) compare the nutritional, hormonal, biochemical, body composition, physical activity, and psychosocial variables in 1-year BMD responders to 1-year BMD non-responders. To accomplish these aims, data from the Bone, Estrogen, Strength Training (BEST) study, a large NIH-funded project, will be used. The original aim of the BEST study was to determine the effects of a 1-year exercise training program and HRT on BMD in postmenopausal women. However, many subjects continued on the exercise program after the 1-year study. Sample sizes for 1-, 2-, 3-, and 4-year data are 266, 213, 185, and 171 (projected), respectively. This database presents a unique opportunity to examine long-term BMD changes in a comprehensive database which includes the volume of exercise performed, leisure-time physical activity, nutritional data, body composition, physical fitness, hormonal data, markers of bone formation and resorption, and psychosocial variables, such as self-esteem, depression, quality of life, social support, and barriers to exercise. The present study will use the existing BEST data as well as the follow-up data for 2-, 3-, and 4-year effects. The information gained from these analyses will enable the prediction of BMD changes well after the effects of the bone remodeling transient. The study will assist in a better understanding of the pattern of the BMD response over longer periods of time and will be able to identify factors that may relate to the likelihood of responding to a given treatment.

▶ Title: *Ethnic Differences in the Management of Osteoarthritis* NIAMS
P.I.: C. Kent Kwoh, M.D.
Institution: University of Pittsburgh, PA
Grant No.: 1 R01 AR50265-01
Study Type: Clinical
Amount: $300,000

The proposed study seeks to examine factors that may provide the basis for health disparities in the utilization of elective total joint replacement, and builds on two federally funded studies. The first examines ethnic differences in the management of osteoarthritis (OA) among male veterans. The second, the Study of Healthy Aging: Body Composition (Health ABC) study, is a NIA-funded longitudinal evaluation focusing on two population-based cohorts of individuals between the ages of 70 to 79 recruited from the Pittsburgh, PA and Memphis, TN metropolitan areas. The overall goal of this research is to better understand the reasons behind ethnic variations in the utilization of lower extremity total knee arthroplasty (TKA) or total hip arthroplasty (THA). The proposed study will examine the health beliefs, practices, preferences, and perceptions of African American women and men, as well as white women and men with knee or hip OA and how these factors may influence consideration of TKA/THA. A cross-sectional study design will be utilized to examine the following Specific Aims: 1) to examine ethnic/gender differences in individuals' self-report of symptoms and functional status among individuals with OA of similar radiologic severity; 2) to examine ethnic/cultural differences in perceptions of the efficacy of specific treatment options for arthritis and willingness to have TKA/THA; 3) to examine gender differences in perceptions of specific treatment options for arthritis and willingness to have TKA/THA; and 4) to examine ethnic/gender differences in provider-level factors related to access to TKA/THA. The 518 individuals from the Health ABC study with symptomatic and radiographic knee OA and 271 with symptomatic and radiographic hip OA will be surveyed. Regarding Specific Aims 1 and 2, major variables that may confound the relationship between ethnicity or gender and willingness to have joint replacement include understanding the risks and benefits of joint replacement; pain coping strategies; perceptions of the efficacy of a specific treatment option such as prayer, and perceptions of health care. The proposed study is unique in that it will examine ethnic and gender differences in the management of OA across patients with varying disease severity, focusing on specific factors that may explain health disparities.

▶ Title: *Longitudinal Changes in Hip Geometry and Skeletal Muscle* NIAMS
P.I.: Zhao Chen, Ph.D.
Institution: Arizona Board of Regents, University of Arizona, Tucson
Grant No.: 1 R01 AR049411-01 A1
Study Type: Clinical
Amount: $222,980

This study will be conducted among a large multiethnic cohort (N = 11,432) from the nationwide Women's Health Initiative (WHI), which includes an observational study and four clinical trials. The age range of this cohort is between 50 to 79 years at the baseline, and it has multiple minority groups: 1,583 black, 739 Hispanic, and 149 Native American women. By 2005, the maximal follow-up time of this cohort will be 9 years. Dual-energy x-ray absorptiometry (DXA) is used to measure bone mineral density (BMD) and body composition The randomized clinical trials and longitudinal nature of the WHI study provide a unique opportunity to investigate:
1) treatment effects of menopausal hormone therapy (MHT) and calcium plus vitamin D supplementation on hip structural geometry; 2) longitudinal changes in skeletal muscle mass as a factor in hip fragility; and 3) ethnic differences of mean and rates of changes in hip geometry and muscle mass. Special computer software will be used for analyzing hip scans by dual-energy x-ray absorptiometry (DXA). Cross-sectional area, subperiosteal width, estimated endocortical

diameter, estimated mean cortical thickness, buckling ratio and section modulus at the femoral neck, at the intertrochanteric, and the femoral shaft regions will be assessed. Magnetic resonance imaging (MRI) scans will be used as references to calibrate total and leg skeletal muscle measurements from DXA subregion analyses. Prevalence rates of sarcopenia (low muscle mass) among each age and ethnic group will be studied. Mixed Effects Models will be used to analyze the longitudinal data. Recourses that the WHI program will provide include DXA scans, fall and fracture data, and information on covariates. Since the majority of data collection work has been or will be done by the WHI, the investigators will be able to cost-effectively test multiple important scientific hypotheses in this study. The novel approaches in this ancillary study will enhance scientific contributions of the WHI program. The significance of the proposed study is that it may demonstrate the utility of bone structural analysis in addition to bone mass measurements for understanding ethnic differences in fracture risk and/or for assessing the effect of pharmacologic therapy (i.e., CaD) on bone health. Furthermore, if the muscle variables are found to be related to bone structure in the proximal femur and the risk of fall, then it may be important to further test whether interventions that increase muscle mass in this region will prevent hip fracture.

▶ Title: *Bone-sparing by Ca Salts with and without Extra Phosphorus* NIAMS
P.I.: Robert P. Heaney, Ph.D.
Institution: Creighton University, Department of Medicine, Osteoporosis, Omaha, NE
Grant No.: 1 R01 AR048846-01A1
Study Type: Clinical
Amount: $75,000

Bone mineral is basically calcium phosphate, and both elements (Ca and P) are required for bone acquisition. Typical Ca intakes in the United States are lower than current recommendations, and typical P intakes, higher. To test the possible importance and value of supplementing both of the components of bone mineral in support of anabolic therapy of osteoporosis, we propose a 1-year randomized trial, comparing, in two groups of teriparatide-treated postmenopausal osteoporotic women, calcium supplements with and without extra phosphorus (i.e., Ca phosphate vs. Ca carbonate). The principal outcome measure will be change in bone mineral content over the 1 year of the trial. A secondary outcome is measurement of bone resorption biomarkers so as to assess whether the phosphate salt elevates remodeling relative to the carbonate salt. A finding of superiority of the phosphate-containing Ca supplement would provide evidence leading to a cost-neutral change in Ca sources and a corresponding improvement in osteoporosis co-therapy (and possibly osteoporosis prophylaxis as well).

▶ Title: *Calcium Absorption in Caco-2 Cells: Molecular Mechanism* NIDDK
P.I.: James C. Fleet, Ph.D.
Institution: Purdue University, West Lafayette, IN
Grant No.: 2 R01 DK054111-06A2
Study Type: Basic
Amount: $200,000

The research will clarify the mechanisms used by 1,25 (OH)2D to promote calcium absorption and to determine how dysfunction in the regulatory control of intestinal calcium absorption during aging or due to menopause leads to reduced absorption efficiency and, ultimately, low bone density. Recent research demonstrates that 1,25 (OH)2D rapidly activates scr kinase, protein kinase C (PKC), and MAP kinases and that inhibition of these kinases blunts 1,25 (OH)2D-mediated activation of the CYP24 gene. The goal of the proposed research is to determine how the adaptive increase in intestinal calcium absorption due to 1,25 (OH)2D-dependent, vitamin D receptor (nVDR)-mediated gene activation is influenced by the basal or induced activity of these kinases.

▶ Title: *Bone-sparing Effects of Soy Phytoestrogens in Menopause* NIAMS
P.I.: Silvina Levis, M.D.
Institution: University of Miami School of Medicine, Department of Medicine, FL
Grant No.: 1 R01 AR048932-01A1
Study Type: Clinical
Amount: $100,000

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years is well established. Although hormone replacement therapy (HRT) can spare women some of these complications, the Women's Health Initiative's findings indicate significant potential health risks, risks that prompt more and more women to turn from prescribed HRT to over-the-counter products in the hope that soy phytoestrogens and other "estrogens" from natural sources can replace prescription estrogens in terms of benefits while sparing critical side effects. In spite of the fairly widespread and now rapidly growing use of phytoestrogens, major gaps remain in our knowledge of their long-term efficacy and safety. It is proposed to conduct a Soy Phytoestrogens As Replacement Estrogen (SPARE) study in young menopausal women to evaluate the effectiveness of a 2-year treatment with purified soy isoflavones in preventing bone loss. The study will also explore the effectiveness of oral isoflavones in preventing menopausal symptoms and other changes associated with estrogen deficiency. The study will characterize the actions of a defined preparation of soy isoflavones in humans and will correlate these actions with the circulating serum levels of the principal isoflavone metabolites, providing new insights on their long-term biological actions. This 5-year study will provide a foundation of knowledge from which menopausal women can begin to make more informed decisions regarding HRT and menopausal signs and symptoms.

Neurology

▶ Title: *Sex Differences in Dopamine Systems* NINDS
P.I.: Arthur P. Arnold, Ph.D.
Institution: The Regents of the University of California, Los Angeles
Grant No.: 1 R01 NS045966-01
Study Type: Basic
Amount: $100,000

The proposal has the long-term goal of determining the factors that cause sex differences in structure, function, and susceptibility to disease in mesencephalic dopamine systems. The studies will investigate the cellular and molecular mechanisms by which sex chromosome genes induce sex differences in the phenotype of dopaminergic neurons *in vivo* and *in vitro*. Studies will determine whether the sex chromosome effect is due to genes on the X or Y chromosomes; whether steroid hormones of the Sry gene participate in the induction of sex differences; when during development the sex chromosome effect occurs, whether the sex chromosome effect is direct or indirect on dopamine neurons; the cellular mechanisms of the sex chromosome effect; and whether the sex chromosomes contribute to sex differences in the development and adult structure of the nigrostriatal dopamine system *in vivo*. The proposed studies will contribute to an understanding of the principles of sexual differentiation of the brain. At issue are the molecular mechanisms by which male and female brains differ, which is relevant to the biological basis of abnormalities of sexual differentiation, and to the explanation of sex differences in neurological and psychiatric disease, not only of those that affect dopamine systems (e.g., Parkinson's disease, Tardive Dyskinesia, Tourette's syndrome, schizophrenia), but other sexually dimorphic diseases as well (e.g., multiple sclerosis). Understanding sex differences in brain function will help develop sex-specific strategies for treatment of brain diseases.

Nutrition

▶ Title: *Altered Calcium and Vitamin D Metabolism in Premenstrual Dysphoric Disorder* NIDDK
P.I.: Susan Thys-Jacobs, M.D.
Institution: St. Luke's–Roosevelt Hospital Center, New York, NY
Grant No.: 1 R01 DK57869-03
Study Type: Clinical
Amount: $100,000

Premenstrual dysphoric disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand more completely the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long-term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 with PMDD and 35 controls. Following 2 months of baseline symptom documentation, women with PMDD and controls with be enrolled in a 9-month observational period with frequent hormonal samplings, urinary collections, and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

Obesity/Overweight

▶ Title: *Look AHEAD (Action For Health in Diabetes)* NIDDK
Institution: Wake Forest University (coordinating center), Winston Salem, NC, Johns Hopkins University, Baylor College of Medicine, University of Colorado Health, University of Washington, University of Tennessee, St. Lukes–Roosevelt Institute, University of Alabama at Birmingham, The Miriam Hospital, Pennington Biomedical Research, University of Texas Health Science, University of Minnesota, University of Pittsburgh, Massachusetts General Hospital, University of California–Los Angeles, University of Pennsylvania, and Southwest American Indian Center (12 clinical centers)
Grant No.: 5 U01 DK57136
Study Type: Clinical
Amount: $100,000

Look AHEAD is a multicenter, randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education, and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke, and cardiovascular death.

Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life, and psychological outcomes. The cost and cost effectiveness of the lifestyle intervention relative to diabetes support and education will be assessed.

▶ Title: *Dysregulated Muscle Lipid Metabolism in African Americans* NIDDK
P.I.: Ronald N. Cortright, Ph.D.
Institution: East Carolina University, Greenville, NC
Grant No.: 1 R21 DK65183-01
Study Type: Clinical
Amount: $139,500

The prevalence of obesity and diabetes is greater among African American women (AAW) than Caucasian women (CW) in the United States. Although environmental factors may be influential, obese AAW have been shown to possess inherent metabolic defects that suppress lipid oxidation by skeletal muscle. More startling, however, is the emerging evidence that these defects may pre-exist in non-obese AAW, predisposing this racial group toward a more rapid onset of fat gain vs. CW. This is fundamentally important because the resultant increase in intramuscular lipid content is strongly linked with insulin resistance and diabetes. Despite the significance of these findings, the cellular mechanisms to explain this racial/ethnic specific metabolic dysfunction remain undefined. Our primary hypothesis is that pre-obese/diabetic AAW possess skeletal muscle with an inherent impairment in the capacity to oxidize long-chain fatty acids (LCFA), leading to a cytotoxic accumulation of bioactive lipids, and precipitation of insulin resistance and diabetes. However, in lean CW, endurance exercise training (EET) stimulates mitochondrial biogenesis, elevating the muscles capacity to oxidize LCFA. The secondary hypothesis is that AAW will respond to EET by increasing the capacity of skeletal muscle to oxidize lipids, thus reducing the propensity toward developing obesity and diabetes. The aims of the investigation are: 1) to identify the pre-existing cellular site(s) of dysfunction in skeletal muscle LCFA oxidation in lean AAW, and 2) to determine whether AAW are responsive to EET. To accomplish the aims, the investigators will study 12 sedentary, lean AAW and CW matched for age, BMI (< 25 kg/m2), and menstrual status. Obese subjects from both races will be assessed for comparisons. Skeletal muscle LCFA oxidative capacity will be measured by trapping labeled 14CO2 derived from oxidation by intact muscle strips and homogenates (rectus abdominus) in order to identify the specific cellular defects in lipid metabolism as being due to: 1) pre-mitochondrial events, 2) mitochondrial activation of LCFA to acyl-CoA, 3) the transport of LCFA across the mitochondrial membrane, and/or 4) the post-transport mitochondrial oxidative system. Measures of whole body insulin sensitivity will be made to determine the strength of association between the status of skeletal muscle lipid metabolism and insulin action. A subset of subjects from aim 1 and new recruits will undergo 7 days and 8 weeks of EET (cycling) to determine the impact of chronic muscle activity (vastus lateralis) on mitochondrial biogenesis, oxidation of LCFA, and insulin action in AAW. The findings will be used for subsequent research to achieve the long-term objective of understanding the mechanism(s) that underlie the greater morbidity and mortality associated with obesity and diabetes in AAW.

Ophthalmic Diseases

▶ Title: *Incidence of Late Macular Degeneration in Older Women* NEI
P.I.: Anne L. Coleman, M.D.
Institution: University of California–Los Angeles
Grant No.: 1 U10 EY13626-01A1
Study Type: Epidemiologic (case-control)
Amount: $230,000

Age-related macular degeneration (ARM) is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14-year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted, health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5,482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5 percent of these women have photographically validated late ARM, 41.5 percent have early ARM, and 54 percent have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEI-VFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30 percent of the eyes with ARM and 10 percent of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

▶ Title: *Visual Dysfunction and Quality of Life in Multiple Sclerosis* NEI
P.I.: Laura J. Balcer, M.D.
Institution: University of Pennsylvania, Philadelphia
Grant No.: 1 R01 EY13273-02
Study Type: Clinical Cohort Study
Amount: $125,000

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in

patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1) define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2) determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

▶ Title: *Effect of Estrogen on Radiation-included Cataractogenesis* NEI
P.I.: Joseph Dynlacht, Ph.D.
Institution: Indiana University, Indianapolis
Grant No.: 1 R03 EY014627-01
Study Type: Basic
Amount: $147,367

The induction of cataracts is often an unfortunate and unavoidable consequence of conventional radiation therapy for head and neck or ocular tumors, whole-brain irradiation, and total-body irradiation prior to autologous bone marrow transplantation. Though not life-threatening, radiation-induced cataractogenesis represents a potentially serious sequelae of radiotherapy which can require surgical intervention. While the cellular and molecular mechanism(s) of radiation-induced cataractogenesis have not been clearly elucidated, damage to the genome at the time of exposure and subsequent proliferation of the radiosensitive cells in the germinative zone of the lens epithelium likely play a role in the process. Using a rat model, preliminary data has been accumulated, which indicate that estrogen reduces the latent period and may increase the incidence and severity of radiation-induced cataracts. High estrogen levels are artificially induced in non-pregnant women using oral contraceptives, or in postmenopausal women on estrogen replacement therapy, and these groups may be at an increased risk for developing cataracts which are more severe or occur with a more rapid onset. Estrogens regulate several proteins involved in cell cycle control and apoptosis, and it's metabolism results in the production of free radicals which may be genotoxic and mutagenic to mammalian cells. Thus, a novel hypothesis to be tested in the proposed studies is that estrogen alters cell cycle regulation, DNA double strand break induction or repair, and proliferation in irradiated lens cells. The dose-time interactions of radiation and estradiol will be investigated to better understand the mechanism of estrogen action, and determine whether estrogen-modulation of radiation cataractogenesis is estrogen receptor (ER)-mediated using knockout mice that are deficient in either ERa or ERb. The lens has frequently been used as a model for predicting delayed (late) effects in other irradiated tissues. Data obtained from the proposed study may demonstrate that the lens is a useful model for predicting late effects in other estrogen-responsive target tissues. Finally, the efficacy of utilizing a novel technique for small animal irradiations shall also be tested; in this study, using the Leksell Gamma Knife, only one eye shall be irradiated in each of the animals, with the contralateral eye serving as a control.

▶ Title: *Estrogen Receptors and Maintenance of Lens Transparency* NEI
P.I.: Vicki L. Davis, Ph.D.
Institution: Cedars-Sinai Medical Center, Los Angeles, CA
Grant No.: 1 R01 EY014600-01
Study Type: Basic
Amount: $130,093

This is a study of the function of the estrogen receptor with regard to lens transparency using transgenic mice models. The project does not employ any novel concepts, approaches, or methods. However, it is of high impact because it will provide information critical for establishing a rational estrogen-signaling modulation therapy for maintaining lens transparency.

Pain

▶ Title: *Low Back Pain—A Multicenter Randomized Trial* NIAMS
P.I.: James Weinstein, D.O.
Institution: Dartmouth Medical School, Hanover, NH
Grant No.: 5 U01 AR045444-04
Study Type: Clinical
Amount: $100,000

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

▶ Title: *Pain Management in Temporomandibular Joint Disorders* NIDCR
P.I.: Jennifer Haythornthwaite, Ph.D.
Institution: Johns Hopkins University, Baltimore, MD
Grant No.: 1 R01 DE13906-02
Study Type: Clinical Behavioral
Amount: $312,313

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

▶ Title: *Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)* NIDCR
P.I.: James R. Fricton, D.D.S., M.S.
Institution: University of Minnesota, Minneapolis
Grant No.: N01 DE22635
Study Type: Registry
Amount: $100,000

The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR's TIRR) at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the

United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

▶ Title: *Sex Differences in Opioid Analgesia* NIDA
P.I.: Anne Z. Murphy, Ph.D.
Institution: University of Maryland School of Medicine, Baltimore
Grant No.: 1 R01 DA016272-01
Study Type: Basic
Amount: $50,000

Chronic pain afflicts millions of people each year. Opioid-based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animal models of acute pain, the effective dose of morphine is approximately five to ten times greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in Aim 1 will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in Aim 2 will use neural tract tracing techniques to delineate the anatomical organization of the PAG-NRM spinal cord circuit in males and females. Aim 3 will examine the functional organization of this circuit in a model of prolonged inflammatory pain. The PAG is enriched in opioid receptors. Studies proposed in Aim 4 will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. These studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex-based differences in opioid analgesia.

▶ Title: *Trigeminal Pain Mechanisms and Control* NIDCR
P.I.: Jon D. Levine, Ph.D.
Institution: University of California–San Francisco
Grant No.: 5 P01 DE08973-12
Study Type: Basic
Amount: $159,422

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

Physical Activity

▶ Title: *Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease* NHLBI
P.I.: Brian H. Annex
Institution: Medical Center, Durham, NC
Grant No.: 1 R01 HL075752-01
Study Type: Clinical
Amount: $250,000

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5 percent of the U.S. population over 50. Approximately 1/3 of patients with PAD have typical claudication, defined as pain in one or both legs on walking that is relieved by rest. Patients with claudication have a marked impairment in exercise performance similar to patients with NYHA class III heart failure. Goals of treatment for PAD patients include risk-factor modification and antiplatelet drug therapy to address increased cardiovascular mortality risk. Supervised exercise training is the most efficacious treatment to improve walking capacity, demonstrated in many (small) randomized trials. Neither the pathophysiology of claudication nor the mechanism(s) by which exercise training improves walking times in persons with IC are completely understood. It is unknown how long-term exercise training effects skeletal muscle or to what extent skeletal muscle abnormalities in PAD are reversible. Women have been largely underrepresented in mechanistic studies of IC and exercise training. There is an urgent need for clinical research directed towards defining the basis of the exercise training changes induced in PAD patients in order to: 1) provide insights into the general pathophysiology of the exercise impairment in PAD; 2) permit scientifically plausible and testable modifications to currently prescribed exercise regiments to better employ this critical therapeutic modality; and 3) identify novel targets from pharmacotherapy that are capable of inducing the repertoire of molecular responses induced by exercise training.

▶ Title: *Increasing Physical Activity Levels in Low-income Women* NIDDK
P.I.: Barbara J. Speck, Ph.D., R.N.
Institution: University of Louisville, KY
Grant No.: 1 R01 DK63523-01
Study Type: Clinical
Amount: $178,750

This project is aimed at reducing community environmental barriers to physical activity in medically underserved women. The setting for the study is a church-sponsored community center with a nurse-managed clinic that is located in a low-income neighborhood. Pretest data will include psychosocial questionnaire, physiologic (cholesterol, blood pressure), and anthropometric measures. The 6-month intervention will be twofold: 1) provide culturally appropriate educational activities to increase women's comfort level at the community center, and 2) provide multiple culturally appropriate physical activity opportunities utilizing the gymnasium and exercise equipment. The long-term goal is to establish physical activity opportunities for women at this community center that could be adapted at other community centers.

Reproductive Health/Developmental Biology

▶ Title: *Fragile X Mental Retardation Gene Premutation* NICHD
P.I.: Pamela L. Mellon, Ph.D.
Institution: University of California–San Diego, La Jolla
Grant No.: 5 U54 HD12303-23
Study Type: Translational
Amount: $113,000

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X Mental Retardation Gene (FMR1). Interestingly, unaffected carriers, or so-called FRX premutation carriers, show an increased prevalence of premature ovarian failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1 percent of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16 percent. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve, which clearly can impact the cessation of reproductive function. Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

▶ Title: *Development and Differentiation in Reproductive Axis* NICHD
Cooperative Reproductive Sciences Research at Minority Institutions
P.I.: Director—David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, GA
Co-director/Partner—Tony M. Plant, Ph.D., University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA
Grant No.: 5 U54 HD41749-02
Study Type: Basic science, translational, clinical
Amount: $250,000

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health. The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core: Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant; Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann; Grant No. 2–1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson; Grant No. 3–1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran and; Grant No. 4–1U54HD41749-010004 (SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

▶ Title: *Intermediate Outcomes of Hysterectomy and Alternatives* AHRQ
P.I.: Miriam Kuppermann, Ph.D.
Institution: University of California–San Francisco
Grant No.: 1 R01 HS11657-02
Study Type: Outcome Research
Amount: $250,000

The project expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the proposed study are to: 1) determine whether and how intermediate-term (4 to 8) year clinical and quality-of-life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) develop predictive models of treatment choice and satisfaction from a broad array of domains.

▶ Title: *The Biologic Effects of Androgens in Men and Women* NICHD
RFA: Cooperative Reproductive Sciences Research at Minority Institutions (RFA HD-02-012)
P.I.: Shalender Bhasin, M.D.
Institution: Charles R. Drew University of Medicine and Science, Los Angeles, CA
Grant No.: U54 HD041748
Study Type: Basic science, translational, clinical
Amount: $200,000

The Drew Center would serve to strengthen an existing, established, investigative effort between Charles R. Drew University and UCLA. The role of testosterone in normal female physiology is poorly understood and this center would serve to increase our knowledge of the characterization of this hormone in sexual function, body composition and strength, and cognitive ability in women. One project uses the model of hormone-deficient women. Randomized treatment with varying doses of testosterone is proposed to address these important biological questions. Another project will test the hypothesis that female patients with panhypopituitarism would benefit from physiological testosterone replacement. A third project will use an animal model to examine the genetic factors, beyond hormonal effects, that regulate sex differentiation between male and female brains. The fourth project focuses on androgen-dependent stem cell differentiation. Strengths of the center include the expertise and experience of the investigative team, its clinical approach to examine whether testosterone replacement in physiological range can produce meaningful improvements in quality of life, and its unique approach to investigating the molecular basis of sex differentiation.

▶ Title: *MMC/PSU Cooperative Center for Research in Reproduction* NICHD
RFA: Cooperative Reproductive Sciences Research at Minority Institutions (RFA HD-02-012)
P.I.: Ponjola Coney, M.D.
Institution: Meharry Medical College, Nashville, TN
Grant No.: U54 HD044315
Study Type: Basic science, translational, clinical
Amount: $200,000

The Meharry Center would serve to facilitate the development of a reproductive science research center at Meharry Medical College through a strong collaborative partnership with Pennsylvania State University. Studies outlined in these projects will generate knowledge and assess outcomes across the lifespan of women of different ages and racial/ethnic groups: 1) the role of sex steroid

hormones as determinants of bone mineral density in African American females, 2) the influence of oral contraceptives on the growth of uterine fibroids, and 3) the efficacy and safety of metformin and lifestyle factors in the amelioration of polycystic ovary syndrome (PCOS) and its symptomatology in both adolescent and adult females. The overall objective is to determine whether ovarian production of estrogens and progesterone differ among women of diverse racial/ethnic groups and whether these determinants are responsible for racial differences in several positive and negative health outcomes. Strengths of the Center include the innovative aspects of the proposed projects, their experimental designs, and the comparisons of lifestyle interventions and therapeutic regimens.

▶ Title: *Control of Menstrual Bleeding Disturbances in Women* NICHD
P.I.: Ian Stewart Fraser, M.D.
Institution: Sydney Centre for Reproductive Health Research, Ashfield, Australia
Grant No.: 1 R01 HD043192-01
Study Type: Basic
Amount: $35,000

This project will evaluate two promising approaches to the treatment of prolonged and frequent episodes of breakthrough bleeding which sometimes accompany the use of the implantable, progestogen-only implant, Implanon. These erratic episodes of bleeding can be a major reason for discontinuation of use. There is increasing evidence that continuous exposure to progestogens results in a tendency for the endometrium to release active enzymes, called matrix metalloproteinases [MMPs], which can promote premature breakdown of the tissue. Inhibition of the action of these enzymes may stabilize the endometrium and improve the bleeding pattern. A commonly used tetracycline compound, Doxycycline, has strong anti-MMP action and preliminary evidence in a mouse model of menstruation suggests that it may indeed stabilize the endometrium. There is preliminary evidence that a short course of an antiprogesterone, Mifepristone, may also stabilize the endometrium, and it is postulated that a combination of antiprogesterone with estrogen may be even more effective. Preliminary evidence in mice indicates that estrogen exposure of the endometrium in the absence of progesterone strongly inhibits the formation of new blood vessels and simultaneous anti-progesterone exposure will mimic this situation.

▶ Title: *Female Reproductive Organs and Their Innervation* NINDS
P.I.: Raymond E. Papka, Ph.D.
Institution: Northeastern Ohio Universities, Roostown
Grant No.: 1 R01 NS022526-14A1
Study Type: Basic
Amount: $100,000

Two important problems in obstetrics are control of uterine body contractions and cervical dilatation. The long-term goal of this research is to understand neural mechanisms for integration of uterine cervical information and how these play a role in cervical ripening and parturition (act of giving birth), particularly as this relates to pre-term or protracted labor, spinal cord-injured females, and autonomic dysreflexia. Rationale for these studies is that birthing problems are critical obstetric problems; pre-term labor occurs in 5 to 10 percent of pregnancies in North America. Within this context, the aims of this proposal are to elucidate the sensory neural substrate of the uterine cervix and how this substrate relates to physical changes in the cervix during cervical ripening and parturition. We propose that this substrate involves sensory nerves, neurotransmitters, receptors, the hormone estrogen, and controlled neurogenic inflammation and leads to the hypothesis: sensory neurons and transmitters innervating the uterine

cervix are estrogen responsive, plastic, and are critical components participating in tissue rearrangements occurring at cervical ripening and parturition. Specific aims will determine: 1) if there is enhanced synthesis and release of neurotransmitters by sensory neurons innervating the uterine cervix, specifically at cervical ripening and parturition; 2) if there are specific neurochemically identifiable sensory neurons of lumbosacral spinal ganglia activated expressly at cervical ripening and parturition; 3) if estrogen, working through estrogen receptors, influences levels of neurotransmitters in sensory ganglionic neurons innervating the cervix during pregnancy, parturition, and early postpartum; 4) if cervical ripening and parturition entail a controlled neurogenic inflammatory process; and 5) if specific subclasses of small C-type (peptidergic and non-peptidergic) neurons have identifiable roles in cervical ripening and parturition. These studies will utilize *in situ* hybridization, RT-PCR, Western blots, immunohistochemistry, nerve transections, and neurotoxins. Health benefits from understanding involvement of neural mechanisms in the uterine cervix include an increased basic understanding of neuroendocrine coordination of gestational events, including pregnancy, cervical ripening, and parturition; and the possibility of remediating problems, such as pre-term labor, protracted labor, and autonomic dysreflexia. Finally, knowledge of estrogen-responsive sensory neurons has important implications for understanding neuropathic pain syndromes influenced by estrogen levels.

▶ Title: *Protein Tyrosine Kinases in Leiomyomata Uteri* NICHD
P.I.: Jean Wang, Ph.D.
Institution: University of California–San Diego
Grant No.: 1 R01 HD046225-01
Study Type: Basic
Amount: $300,000

In this Request for Applications, the investigators propose that female sex hormones stimulate the expression and/or activation of protein tyrosine kinases to promote uterine cell proliferation and tumor growth, and predict that inhibition of protein tyrosine kinases involved in the proliferation of uterine cells would halt the growth of uterine leiomyomata. This study will survey the expression and activity of protein tyrosine kinases in normal uterine myometrium and leiomyoma specimens procured from women in different ages and racial/ethnic groups. The investigator plans to create a microarray that is suitable for profiling the expression of all 90 human protein tyrosine kinase genes. A strength of the application is the creation of the microarray, which is important and promises to have wide-scale application beyond the study of uterine leiomyomata. Results from this study may identify protein tyrosine kinases that are important for proliferation of uterine leiomyomata.

▶ Title: *Estrogen Dependency of Uterine Leiomyoma* NICHD
P.I.: Ayman Al-Hendy, M.D., Ph.D.
Institution: University of Texas Medical Branch, Galveston
Grant No.: 1 R01 HD046228-01
Study Type: Basic
Amount: $300,000

The hormone-dependent phenotype of uterine leiomyomata suggests that interventions targeting the estrogen receptor-signaling pathway may have therapeutic efficacy. This Request for Applications plans to investigate the immune response and safety of single versus repeated recombinant adenovirus treatment alone or in combination with a selective estrogen receptor

modulator (SERM) in mice, rat, and human leiomyoma cells. The strength and overall conceptual framework of this work is to test the validity and regulatory mechanisms of gene therapy as an alternative to non-surgical treatment for uterine leiomyomata, as well as to further elucidate the molecular mechanisms of estrogen dependency of uterine leiomyomata. This highly innovative research will add to our understanding of the molecular mechanisms of estrogen dependence in this common uterine tumor and may open a new area of investigation and treatment of uterine leiomyomata.

▶ Title: *Collaborative Research Initiative* NICHD
P.I.: Linda C. Giudice, M.D., Ph.D.
Institution: Stanford University, Palo Alto, CA
Grant No.: U54 HD 31398
Study Type: Translational
Amount: $150,000

Endometriosis is a benign, estrogen-dependent, gynecologic disorder that is clinically associated with pelvic pain and infertility and is diagnosed by direct visualization during surgery. Pelvic endometriosis, and thus, eutopic endometrium (i.e., endometrium within the uterus), is presumed abnormal in women with the disease. The abnormality extends to uterine receptivity, supported by high implantation failure and poor pregnancy rates in IVF cycles in women with disease. Recently, using a global gene profiling approach, we identified candidate genes for uterine receptivity in normally cycling women without endometriosis and in women with mild/moderate endometriosis, through a collaborative, multicenter study. The current collaborative research initiative will lay the foundation for clinical translation of the data collected to date, with the following goals: diagnosis of a receptive endometrium for fertility; diagnosis of a non-receptive endometrium in women with endometriosis and infertility; diagnosis of endometriosis; and diagnosis of the stage (severity) of endometriosis in the pelvis.

▶ Title: *Prevalence and Etiological Predictors of Vulvodynia* NICHD
P.I.: Bernard L. Harlow, Ph.D.
Institution: Brigham & Women's Hospital, Boston, MA
Grant No.: 5 R01 HD38428-05
Study Type: Clinical
Amount: $100,000

Vulvodynia is a syndrome of unexplained vulvar itching, burning, and/or pain that causes major physical and psychological distress. It is a diagnosis of exclusion when vulvar discomfort becomes chronic over many months and the presence of any other remediable cause, such as infection or dermatitis, is ruled out. The two major subtypes of vulvodynia—generalized vulvar dysesthesia and vestibulodynia—are often misclassified. Few descriptive or etiologic epidemiological studies have been performed. Thus, the prevalence and incidence in the general population is unknown and no preventable exposures have been identified. A recent NIH-sponsored consensus conference stressed the need to determine the prevalence of vulvodynia and conduct population-based observational studies to identify modifiable risk factors. The applicant has conducted a population-based prevalence survey in more than 400 women that achieved a 70 percent response rate and found that 18 percent of women reported a lifetime history of chronic vulvar symptoms that lasted 3 months or longer. Approximately 8 percent of all women surveyed were currently experiencing these symptoms. In addition, the applicant

conducted a pilot case-control study of 31 women diagnosed with either dysesthetic vulvodynia or vestibulodynia, or a combination of the two within the last 5 years and compared them to 31 similarly aged health women identified from the general population. Cases were, on average, three times more likely to report medical treatments or surgical procedures for conditions that may have influenced perineal pain, or a greater frequency of condom use and use of talcum powder in the genital area that may have lead to mucosal abrasion and inflammation. A survey is being conducted on 16,000 women, 20 to 59 years of age, from the general population to estimate the age-specific prevalence of vulvodynia. From this sample, the applicant will identify 400 cases of vulvodynia, verified through a two-step screening process, and a sample of 400 frequency-matched age and county of residence controls. Structured interviews will assess a wide spectrum of exposures related to trauma. A subsample of 80 cases and 80 controls will receive a clinical examination to confirm the presence or absence of vulvodynia, and also will provide a vaginal lavage and vulvar swab specimen for the assessment of cytokines and the culturing of microbiological organisms. It is hypothesized that various types of vulvar trauma may precede the spontaneous and evoked vulvar pain experienced by women with vulvodynia, and that vulvodynia may be a variant of a specific type of complex regional pain syndrome that is consistent with sensory disturbances, such as mechanical allodynia.

▶ Title: *Vulvodynia Prevalence and Efficacy of Four Interventions* NICHD
P.I.: Gloria A. Bachmann, M.D.
Institution: UMDNJ-RWJ Medical School, New Brunswick, NJ
Grant No.: 5 R01 HD40119-05
Study Type: Clinical
Amount: $100,000

Vulvodynia is a complex, multifactorial chronic pain syndrome that is associated with significant distress and interpersonal. Vulvar vestibulitis and dyspareunia are two common, although not well-understood clinical components or sub-types of vulvodynia. Chronic vulvar pain is experienced by, according to recent surveys, 10 to 15 percent of the female population between 18 and 80. This project is examining the efficacy, outcomes, and cost effectiveness, and associated with four non-surgical interventions for vulvodynia.

APPENDIX D
Office of Research on Women's Health Research Summaries, 2004

Aging

▶ Title: *Phytoestrogens and Aging: Dose, Time, and Tissue* NIA
P.I.: William Helferich, Ph.D.
Institution: University of Illinois, Department of Food Science & Human Nutrition, Urbana
Grant No.: 1 P01 AG024387-01
Study Type: Basic
Award: 195,000

The overall research objective of this grant is to evaluate the potential beneficial or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue and the brain, using well-established laboratory animal models. Although phytoestrogens are consumed by older Americans for their perceived beneficial effects, these estrogenic compounds have not been adequately evaluated for safety, despite increasing consumption of these chemicals at high levels, especially among older women. The theme of this project is that dosage, timing, and duration of exposure will all be determinants of the biological outcome of phytoestrogen exposure in different target tissues. Since both potential risks and benefits need to be evaluated, these studies cannot be conducted in humans for ethical reasons and can best be conducted in appropriate pre-clinical laboratory animal models. The proposed studies provide a systematic evaluation of the role that various regimens of phytoestrogen exposure may have on target organs that are of special relevance in aging, and these studies will also seek to determine the mechanism of phytoestrogen effects on these different target tissues.

▶ Title: *Modulation of Age-related Changes in the Auditory System* NIA
P.I.: James F. Willott, Ph.D.
Institution: University of South Florida, Tampa
Grant No.: 2 R01 AG007554-15
Study Type: Basic
Award: $315,250

The current project has been investigating a method that dramatically ameliorates age-related hearing loss in several inbred strains of mice that serve as models for presbycusis and other forms of progressive sensorineural hearing loss. The treatment involves an augmented acoustic environment (AAE), an extended period of nontraumatic acoustic stimulation for 12 hours each day. Positive effects of AAE treatment include slowing progressive elevation of auditory brainstem response (ABR) thresholds, diminished loss of outer hair cells and spiral ganglion cells, lessened age-related reduction of volume and neuron loss in the anterior ventral cochlear nucleus (AVCN), increased amplitude of the acoustic startle response, and stronger prepulse inhibition (PPI; indicative of the behavioral salience of sounds). However, in demonstrating these findings, the current project has revealed that the effects of AAE treatment are complicated by several factors including sex, frequency spectrum of the AAE; and age or degree of progressive hearing loss at initiation of AAE treatment. The continuation project addresses these factors, focusing on histopathology of the cochlea and AVCN using D2 and B6 mice. Aim 1 will evaluate an observed sex effect in B6 mice: females between 6 to 12 months of age (when fertility and estrogen are declining) exhibit

an acceleration in the rate and severity of hearing loss compared to males. Findings stemming from this aim can help us to better understand sex-related factors that may modulate presbycusis in humans. Aim 2 will elucidate variables responsible for the positive effects of AAE treatment on cochlear tissue using histological methods. The goal is to gain additional insight into mechanisms associated with AAE effects. Aim 3 will study the role of sex hormones and other variables involved in central AAE effects, including the death in AVCN neurons in AAE-treated male B6 mice and neuron protection observed in females. The findings will have implications with respect to possible effects of the acoustic environment (e.g., amplification) on the central auditory system. Aim 4 will evaluate in greater detail the effects of very early initiation of AAE treatment, which has potential clinical implications. The proposed continuation project can help us to better understand progressive sensorineural hearing loss and factors that modulate it, such as sex hormones and age at intervention. The ultimate goal is to develop new approaches for amelioration and treatment of presbycusis and other hearing disorders.

▶ Title: *End-of-Life Care in Assisted-living Facilities* NINR
P.I.: Juliana C. Cartwright, Ph.D.
Institution: Oregon Health Sciences University, Portland
Grant No.: 1 R03 NR008921-01
Study Type: Clinical
Award: $75,499

The purpose of this study is to address the absence of descriptive knowledge about end-of-life (EOL) care in the fastest growing, yet understudied, congregate residential setting for frail older adults, assisted living facilities (ALF). Nationally, it is estimated that death accounts for 28 percent of the annual turnover in ALF residents. Increasingly, dying ALF residents are enrolled in hospice programs. Despite projections that ALFs will surpass nursing homes in occupancy within several years, and estimates that the current national population of 1 million ALF residents will double by 2020, there is limited information on EOL care and hospice involvement in ALFs. Specifically, this study will examine the perspectives of ALP staff and hospice nurses on: 1) how EOL care is provided for ALF residents, and 2) facilitators and barriers to EOL care in ALFs. A qualitative descriptive design will be used. Face-to-face, semi-structured interviews will be conducted with a purposeful sampling of up to 36 ALF and hospice nurses in both rural and urban sites in Oregon. In addition, documents used in EOL care in ALFs will also be analyzed (e.g., flow sheets, protocols). Qualitative content analysis will include the following components: open coding of text data, constant comparative analysis of text data and documents, negative case analysis, theoretical memos, and document trails. Key characteristics of the care activities, similarities and differences in how the activities are performed, and related challenges and barriers will be identified. The end product of this study will be a detailed description of how EOL care happens for ALP residents, from the perspectives of the staffs that provide or supervise this care. The findings, in combination with the investigator's earlier findings from dying residents and their families, will be the basis for developing and testing a model intervention aimed at improving EOL care in ALFs in subsequent research.

▶ Title: *A Fall Prevention Program for High-risk Elderly Women* NINR
P.I.: Jean F. Wyman, Ph.D., R.N.
Institution: University of Minnesota, Minneapolis
Grant No.: 5 R01 NR005107-05
Study Type: Clinical
Award: $100,000

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

▶ Title: *Health, Illness, and Social Life at Older Ages* NIA
National Social Life Health and Aging Project
P.I.: Linda Waite, Ph.D.
Institution: Department of Sociology, Center on Aging, University of Chicago, IL
Grant No.: 1 R01 AG021487
Study Type: Clinical
Award: $250,000

It is well established that social support, particularly marriage, bolsters psychological and physical health as people age. Human sexuality constitutes one essential, but poorly understood, parameter of both healthy aging and social life at older ages. Physicians and public health policymakers lack a scientific base of information for advising older people or designing programs that might promote sexual health, support prolonged independence, relieve anxiety, prevent dysfunction or disease, or address current issues influencing intimate social and sexual relationships among older Americans. The Interactive Biopsychosocial Model (IBM) developed for this research is an extension of Engel's biopsychosocial model. Health is conceptualized as a function of biophysical and psychocognitive dynamics between individuals over time and incorporates social embeddedness in shaping that process. A nationally representative probability sample of 3,000 community-residing women and men, ages 57 to 84, will be followed longitudinally in two waves over 5 years. We will oversample African American and Hispanic adults. Face–to-face interviews and biomarker collection will take place in respondents' homes. Data collection will elicit: 1) demographics; 2) social networks; 3) social and cultural activity; 4) physical and mental health, including cognition; 5) well-being; 6) illness; 7) medications and alternative therapies; 8) history of sexual and intimate partnerships; and 9) patient-physician communication regarding sexuality, sexual identity, functionality, desire, opportunity, and attitudes about sexuality and intimacy. Biomarker collection will include: height, weight, blood pressure, serum (glucose metabolism, HIV, hepatitis, syphilis), urine (gonorrhea, chlamydia, trichomonas), saliva (endocrine evaluation), and sensory testing (vision, hearing, touch, taste, smell). Three specific aims will be addressed: 1) describe health and health transitions of older community-residing Americans, 2) evaluate the relationship between health and older adult sexuality, and 3) examine sexuality within social networks and their sociocultural context.

Alcohol and Other Substance Abuse

▶ Title: *Screening and Brief Intervention of Problem-drinking Women* NIAAA
P.I.: Grace Chang, M.D.
Institution: Brigham and Women's Hospital, Boston, MA
Grant No.: 1 R01 AA014678-01A1
Study Type: Clinical
Award: $100,000

Early identification and intervention among problem-drinking women may avert the more severe, adverse consequences of alcohol abuse and dependence. Among nonpregnant women of childbearing age, the use of alcohol and, in particular, the riskier practices of frequent and binge drinking have not changed since 1995. Moreover, 12 percent of women 60 years and older regularly drink in excess of recommended amounts, and as a group are underscreened and underdiagnosed, despite being the largest group of health care users in the United States. Screening and intervention, while generally effective, have not been adequately tested among women who account for only 27 percent of brief intervention trial subjects since 1995, despite the NIH guidelines on inclusion of women in clinical trials. This is concerning, as women in general are more vulnerable to alcohol's negative effects due to differences in metabolism. The purpose of this randomized trial is to test the effectiveness of screening and brief intervention for risk drinking by nonpregnant women with specific medical problems exacerbated by excessive alcohol consumption. The medical problems are female factor infertility, hypertension, and diabetes, conditions that are costly to treat and difficult to manage. Five hundred fifty-two nonpregnant women with risk drinking (exceeding NIAAA sensible drinking limits of seven drinks a week or one to two drinks per episode) and infertility, hypertension, or diabetes will be randomized to receive either a nurse practitioner-delivered brief intervention using *Personal Steps to a Healthy Choice: A Woman's Guide* or medical treatment as usual. The specific aim of this randomized clinical trial is to test the hypothesis that 45 percent of the women who receive the medically oriented brief intervention and 30 percent of the control group will achieve NIAAA sensible drinking limits in the 12 months after study enrollment.

▶ Title: *Alcohol Pharmacogenetics in Mexican Americans* NIAAA
P.I.: Yu-Jui Yvonne Wan, Ph.D.
Institution: The University of Kansas Medical Center, Kansas City
Grant No.: 2 R01 AA012081-05A1
Study Type: Basic
Award: $100,000

Representing one of the fastest growing ethnic groups in the United States, Hispanics accounted for 12 percent of the nation's population by March 2000, and suffer from higher rates of alcohol-related problems as compared with those from other ethnic backgrounds (e.g., Caucasians and African Americans). This notwithstanding, genetic factors that might contribute to such risks remain poorly understood. Building upon the research infrastructure that has been established, this research will systematically explore and examine genetic mechanisms for alcoholism in Mexican Americans. This ongoing research program has started to identify unique genetic patterns that might be in part responsible for the heightened risk for alcoholism and alcohol associated health problems in this population. These include: I) extremely low allele frequency for both ALDH2*2 (aldehyde dehydrogenase) and ADH2*2 (alcohol dehydrogenase); 2) a relatively high rate of ADH3*2 and CYP2E1 c2 (cytochrome P4502E1) alleles; 3) association of ADH3*2, ADH2*1, DRD2 (dopamine receptor -141C Del/Ins) and serotonin transporter gene-linked polymorphic region (5-HTTLPR) with alcoholism; 4) a strong association of ADH3*2 and ADH2*1

alleles with binge drinking; and 5) association of the DRD2 Taq1 A and 1B alleles with early age of onset for drinking. In this new funding cycle, the investigators plan to further pursue and clarify the meaning of these findings. Specifically, they will: 1) expand the study to include Mexican American women with alcohol problems; 2) further examine the role of these polymorphisms, as well as their potential interactions, in relation to risks for alcoholism in Mexican American populations; 3) examine the role of these risks in relationship with the severity of alcoholism, i.e., binge drinking and early onset of drinking; and 4) characterize and determine the haplotype of DRD2 in association with drinking in Mexican Americans, and assess the relative advantage of haplotype vs. allelic analysis in delineating risk factors contributory to the development of alcoholism. This study will be the first to systematically examine how genetic factors modulate alcohol dependence and abuse in Mexican Americans. Results derived from such a study should not only provide for a better understanding of alcohol use and abuse among Mexican Americans, but also contribute towards a knowledge base regarding ethnic differences in alcohol pharmacogenetics and mechanisms that might be responsible for the high rate of alcoholism in this minority population.

▶ Title: *Reducing Alcohol and Risks Among Young Females* NIAAA
P.I.: Lydia N. O'Donnell
Institution: Education Development Center, Inc., Newton, MA
Grant No.: 5 R01 AA014515-02
Study Type: Clinical
Award: $150,000

An intervention study will be undertaken to characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African American and Latina adolescent females who are at high risk for HIV, AIDS, and other infections. Past research by the investigative team has documented that nearly 10 percent of females in our target population are at risk in 7th grade and more than half by spring of 10th grade. Although alcohol use is more comparable with national figures, the combination of early alcohol and risky behavior is troubling, yet underaddressed by existing interventions. This randomized experiment will test a theoretically derived and empirically grounded "selective" intervention that specifically targets high-risk young adolescent females. The intervention builds upon a promising strategy for influencing adolescents: parent education. Three parenting mechanisms shown to influence adolescent risk behavior will be targeted: parental monitoring, household rule setting, and communication.

Cancer

▶ Title: *Culture and Cancer Disparities: The Case of Latino Women* NCI
P.I.: Hector Betancourt, Ph.D.
Institution: Loma Linda University, CA
Grant No.: 1 R21 CA101867-01A1
Study Type: Basic
Award: $162,000

The aims of this research are to identify aspects of culture associated with variations in breast and cervical cancer screening among Latino women, to develop psychometrically appropriate instruments to measure those cultural variables in English and Spanish, and to examine hypothesized relationships among the identified cultural factors, relevant psychological processes, and cancer screening. Although the focus is on culture, relations to other factors (e.g., age, access to health care, and socioeconomic status) will also be examined. The research is guided by an approach

to the study of culture proposed by the investigators to study the role of culture in psychological functioning and behavior. The instruments to be developed are also expected to contribute to the long-term goal of developing a model that may effectively guide research and intervention concerning not only ethnic disparities in cancer screening but in health behavior in general, with Latino as well as with other culturally diverse populations. Although the immediate focus is on Latino women, Anglo (non-Latino white) women are included as the mainstream comparison group in order to satisfy methodological and practical requirements associated with the comparative study of culture. Participants will be recruited from the population of Latino and Anglo women living in San Bernardino County, Southern California, or any of the surrounding counties in Region 5 of the California Statewide Cancer reporting system. Three distinct methodologies will be utilized. First, the methods for the study of subjective culture will be used to identify specific aspects of culture relevant to cancer screening among Latino and Anglo women. Content analyses of open-ended interviews and focus groups will be performed to identify the relevant aspects of culture and to generate items for the cultural instruments to be developed. Second, conventional psychometric procedures and statistical techniques will be applied to the development and validation of quantitative instruments to measure the cultural factors identified as relevant to cancer screening. Finally, survey methodology and multivariate quantitative methods of analyses will be used to test a hypothesis concerning the relationships among cultural factors, mediating psychological processes, and breast/cervical cancer screening in Latino as well as mainstream Anglo women.

▶ Title: *Modulation of a Breast Cancer Pathway by Pregnancy* NCI
P.I.: Teresa A. Rose-Hellekant, D.V.M., Ph.D.
Institution: University of Wisconsin, Madison
Grant No.: 1 R21 CA106284-01
Study Type: Basic
Award: $133,650

Full-term pregnancy early in life reduces the lifetime risk of breast cancer in women, and in rodents protects against chemically induced mammary cancer, suggesting that rodents may serve as a good model for this effect in humans. However, the effect of pregnancy on transgene-induced carcinogenesis cannot yet be determined in transgenic mice. Traditional transgenic mouse models of mammary cancer employ gene-targeting elements that are upregulated by hormones at puberty, during pregnancy and lactation; the upregulation of transgene expression by pregnancy complicate attempts to study the effects of pregnancy on transgene-induced mammary cancer. In addition, transgene expression in traditional transgenic mice occurs in nearly all mammary epithelial cells, and is active throughout life. This feature does not mimic the spatial pattern of carcinogenic gene alterations in human breast, which typically is focal rather than widespread. Our purpose is to develop a novel transgenic approach that can be used to precisely and independently regulate when transgene expression is "turned on" in the mammary epithelium (specifically, after the completion of pregnancy), and in a focal pattern that mimics the upregulation of breast cancer relevant genes in human disease. To accomplish these goals, the investigators will establish transgenic mice with following characteristics: 1) timing of onset of TGFα expression is regulatable, 2) TGFα expression is activated irreversibly in a controllable fraction of mammary epithelial cells, and 3) TGFα is under the control of an estrogen and prolactin nonresponsive promoter that permits evaluation of the effect on lesion development of hormonal modulation. This application has the following specific aims: *Aim 1*. Develop transgenic mice that permit manipulation of TGFα expression in mammary epithelium; and *Aim 2*. Establish how prior pregnancy affects TGFα-induced mammary tumorigenesis.

▶ Title: *Clinical Trials of Two Human Papillomavirus-like Particle Vaccines* NCI
P.I.: Douglas R. Lowy, M.D.
Institution: National Cancer Institute, Bethesda, MD
Grant No.: 1 Z01 BC09052
Study Type: Clinical
Award: $600,000

Worldwide, cervical cancer annually accounts for over 400,000 incident cases, resulting in approximately 200,000 deaths. The impact of this disease is particularly devastating in developing countries where women are medically underserved and access to Pap smear screening is not readily available. To address this major issue in women's health, the National Cancer Institute (NCI) and the Office for Research on Women's Health is launching a large, double-blinded, randomized clinical trial to evaluate whether vaccination with the bivalent HPV16/18 VLP-based vaccine developed at the NCI and manufactured by GlaxoSmithKline will protect against the development of histopathologically confirmed, incident CIN2+ (cervical intraepithelial lesion grades 2/3), adenocarcinoma *in situ*, and invasive cervical cancer. This pivotal efficacy trial will be conducted in Costa Rica, an area with high rates of cervical cancer. Approximately 20,000 young women will be invited to join the trial, with 12,000 to 15,000 women expected to participate. Eligible women who agree to participate will be administered three doses of either a control vaccine or the HPV 16/18 VLP vaccine over a 6-month period and will be followed for 4 years. The trial is expected to extend through 2009. It is hoped that results from this effort will support licensure of a prophylactic HPV16/18 vaccine that protects against the development of HPV16/18-induced cervical cancer and its precursors.

Cardiovascular Disease

▶ Title: *Genetics of Early-onset Stroke* NINDS
P.I.: Steven J. Kittner, M.D.
Institution: University of Maryland, School of Medicine, Department of Neurology, Baltimore
Grant No.: 5 R01 NS045012-02
Study Type: Clinical
Award: $300,000

The long-term objective of this application is to characterize the genetic basis for ischemic stroke susceptibility in order to develop more effective prevention and treatment strategies. Current evidence suggests that the genes encoding the thrombomodulin-protein C and fibrinolysis systems are promising candidate stroke susceptibility genes because of their pivotal importance in thrombosis regulation and response to inflammation. The researchers postulate that: 1) novel genetic variants in the thrombomodulin, endothelial protein C receptor, and plasminogen activator inhibitor-1 genes predispose to the development of stroke, particularly infection-associated stroke; and 2) endothelial protein C receptor polymorphisms are associated with large vessel stroke, while thrombomodulin polymorphisms are associated with lacunar (small vessel) stroke. To obtain a sample size adequate to test these hypotheses, we propose a population-based, case-control study of ischemic stroke (1,033 cases and 1,064 controls) among young African American and Caucasian men and women. To complement an existing sample of female cases and controls, male cases (n = 600) will be recruited using a network of 59 hospitals in the Baltimore-Washington area. Age-, gender-, and race-matched controls (n = 600) will be recruited by random-digit dialing. A neurologist panel will perform stroke phenotyping. Historical risk factor data and blood samples for genetic studies will be obtained at a face-to-face interview. A comprehensive molecular analysis of the coding, promotor, and intronic regions of the three candidate genes will be performed to determine if sequence variation in these loci is associated with stroke. In addition to analyses

of individual polymorphisms, intragenic haplotypes will be constructed and common haplotypes tested for association with stroke. Population substructure analysis will be used to identify and account for population stratification bias in the analyses. The proposed study will complement other associated studies of older stroke patients and will be a continuing resource for understanding the genetic basis of stroke risk.

▶ Title: *Altered Glucose and Lipid Metabolism In Obesity and Cardiovascular Disease* NHLBI
P.I.: Maureen J. Charron
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 5 R01 HL073163-02
Study Type: Basic
Award: $200,000

This application proposes studies in mice to examine metabolic disturbances and cardiovascular disease in animals that express only one functional copy of the insulin-stimulated GLUT4 transporter (a mouse model of type 2 diabetes), and hypothesizes that metabolic and cardiovascular changes may be mediated by altered expression of adipocyte-specific Acrp30 (adiponectin). The specific objectives of this proposal are: 1) to understand the molecular mechanisms underlying the metabolic changes that specifically affect male, but not female, GLUT4+/- mice or GLUT4+/- mice that overexpress GLUT4 in muscle; 2) to test genetically whether correction of Acrp30 downregulation in male GLUT4+/- will prevent or delay the onset of insulin resistance, visceral obesity, and/or cardiovascular disease (CVD). Additionally, they will test whether complete lack of circulating Acrp30 in Acrp30-/-mice will provoke metabolic disturbance in female GLUT4+/- and exacerbate disease in male GLUT4+/- mice; 3) to assess the effects of high-fat, diet-induced changes in disease progression in GLUT4+/- compared to C57BL/6J mice; and 4) to determine transcripitional and translational changes in white adipose tissue (WAT) associated with visceral obesity and alterations following treatment with thiazolidinedione insulin sensitizers in hope of identifying novel therapeutic targets. Combined, this approach will provide a comprehensive systematic characterization of a mouse model of obesity-associated CVD derived from early impairment of insulin-mediated glucose flux into WAT, and directly address, for the first time, whether alterations in Acrp30 influence disease progression.

Craniofacial

▶ Title: *Brief Focused Treatment for Temporomandibular Disorders: Mechanisms of Action* NIDCR
P.I.: Mark D. Litt
Institution: University of Connecticut, School of Medicine, Farmington
Grant No.: 5 R01 DE014607-02
Study Type: Clinical
Award: $100,000

Temporomandibular disorders (TMD) is a widespread chronic pain condition. Successful psychosocial treatments for TMD have been developed, but the mechanisms by which these treatments achieve their effects are not well known. The goal of this project is to evaluate the possible mechanisms responsible for treatment gains in TMD treatment. Men and women (n = 106) with complaints of chronic facial pain for at least 3 months' duration will be recruited from the University Dental Clinics and from the community via advertisements and randomly assigned to either a Standard Conservative Treatment (STD) employing an intraoral splint plus anti-inflammatory agents, or to a Standard Treatment plus Cognitive–Behavioral Treatment Program (STD+CBT),

that will include standard treatment but also focus on changing self-efficacy and decreasing catastrophization. Both treatments will entail six clinic visits. Dispositional and situational variables derived from a comprehensive model of pain coping will be measured before and after treatment. The situational variables, including coping responses, mood states, situational appraisals, and self efficacy, will be measured in an experience sampling paradigm four times daily using a handheld computer. This will be done to minimize retrospective biases that may have hampered earlier studies of treatment process. Dependent variables will be self-report measures of distress, pain, and interference with activities, as well as blood plasma levels of cortisol and selected cytokines, measured at the end of the 6-week treatment period, and at followup points thereafter up to a 12-month followup. It is expected that the STD+CBT treatment will result in measurable changes in constructs, such as self efficacy and catastrophization, and that these changes will be related to improved outcomes compared to the STD controls. It is also expected that outcome differences between groups will be associated with changes in inflammatory mediators (cytokine levels). Finally, it is suggested that changes in situational treatment process variables will be associated with changes in cytokine levels. The results may indicate the true active mechanisms of successful TMD treatment. If these mechanisms can be successfully identified, it would have important implications for the development of more effective treatment programs.

▶ Title: *Genotype and Temporomandibular Joint Disorders Vulnerability Types* NIDCR
P.I.: Christian S. Stohler
Institution: University of Michigan at Ann Arbor
Grant No.: 5 R01 DE 015396-02
Study Type: Basic, clinical
Award: $100,000

Temporomandibular joint disorders (TMJD) represent a major health problem and persistent TMJD pain is difficult to manage successfully. The majority of cases involve muscle. Laboratory evaluations proposed in this application permit new and critically important insight into the pathogenesis of persistent TMJD pain. The use of approaches from several different scientific disciplines, such as genetics, endocrinology, neurobiology of pain, and imaging of peripheral tissue, are proposed to probe and understand the system response of human subjects with respect to disease characteristics of TMJD and for which measurement opportunities in animals are limited. Based on supporting data, this research aims to provide new knowledge regarding the significance of a candidate gene that appears to exert a strong effect on critical hallmark features of persistent TMJD muscle pain. Because sensitivity to pain and inhibition of pain are traits of considerable variability, the effect of this gene on subject's response characteristics to experimentally induced jaw muscle pain will be studied. Furthermore, because women in their reproductive age make up the majority of patients treated with TMJD, the proposed research also focuses on whether estrogen significantly alters the system's response in subjects of a particular genotype.

▶ Title: *Neuronal Plasticity Related To Temporomandibular Joint Disorders and Fibromyalgia* NIDCR
P.I.: Dean A. Dessem
Institution: University of Maryland, Baltimore
Grant No.: 5 R01 DE 015386-02
Study Type: Basic
Award: $100,000

The long-term objective of this project is to elucidate the role of craniofacial primary afferent neurons in musculoskeletal disorders such as temporomandibular disorders and fibromyalgia (FM) using animal models. Two hypotheses are proposed: *Hypothesis 1*: Masticatory muscle

inflammation increases the number of trigeminal ganglion (TG) muscle afferent neurons that express substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin-1 receptor (NK-lr), and CGRP receptor (CGRPr). This increase involves a phenotypic switch in which muscle primary afferent neurons that do not normally express neuropeptides express SP, CGRP, NK-lr, and CGRPr following inflammation. It is proposed that this change contributes to muscle allodynia and hyperalgesia and can be modulated by pharmacologic manipulations thus providing insight into therapeutics for deep-tissue pain. This hypothesis will be tested by quantifying the distribution of TG muscle afferent somata and peripheral axons containing SP, CGRP, NK-lr, and CGRPr in three groups: i) control, ii) inflamed muscle, iii) inflamed muscle with intervention (anti-nerve growth factor, NK-lr, and CGRPr antagonists). This hypothesis will also be tested by determining the levels of CGRP, SP and gene expression for CGRP, SP within the TG using radioimmunoassay, and reverse transcriptase polymerase chain reaction. *Hypothesis 2*: SP and CGRP alter the functional properties of TG muscle afferent neurons in part by evoking spontaneous activity and increasing their excitability. It is predicted that substantially more group II, III, and IV TG muscle afferent neurons will be modulated by SP and CGRP following inflammation and that these functional alterations can be modulated pharmacologically. This hypothesis will be tested by characterizing the 1) spontaneous and evoked activity, and 2) active and passive membrane properties of TG muscle afferent neurons prior to muscle inflammation, following muscle inflammation, and following muscle inflammation combined with pharmacological intervention. This will be achieved using intracellular electrophysiological recordings from masseter muscle afferent neurons in a trigeminal ganglion-masseter nerve *in vitro* preparation. Determination of soma size, axon diameter, and SP, CGRP immunoreactivity for physiologically characterized TG muscle afferent neurons will also test Hypothesis 1. Because a gender difference is reported for TMD and FM, both hypotheses will be tested in males, estrous females, and diestrous females.

▶ Title: *Estrogen Regulation of Inflammation Related to Temporomandibular Joint Disorders* NIDCR
P.I.: Phillip R. Kramer
Institution: Texas A&M University Health Science Center, College Station
Grant No.: 5 R01 DE015372-02
Study Type: Basic
Award: $100,000

The long-range goal of this research is to identify and characterize genes through which steroidal hormones affect the onset and/or severity of human disease. The objective is to determine a gene in macrophages affected by estrogen withdrawal, as seen postpartum and at menopause, that functions in immune processes. The central hypothesis is that changes in estrogen concentrations directly regulate IgG Fc gamma receptor III-A (CD16a) expression resulting in a modulation of pro-inflammatory cytokine production and/or release from macrophages upon receptor binding. This hypothesis is based on recent findings *in vitro* that: *Aim 1*: the level of Fc gamma RIIIA transcript increased in macrophage-like THP-1 cells and in primary, peripheral blood macrophages after estrogen removal; and *Aim 2*: that the observed increase was dependent on transcription. The hypothesis also includes data from another lab that binding of Fc gamma RIIIA by anti-Fc gamma RIll monoclonal antibodies stimulates macrophage TNF-alpha and IL-1 alpha release. Fc gamma RIIIA is a receptor that selectively binds IgG molecules, an important rheumatoid factor (RF) in auto-immune disease. Collectively, these data suggest that RF binding of this receptor stimulates cytokine release in rheumatoid arthritis and associated temporomandibular joint disorders (TMJD). To test the central hypothesis, aim one will characterize macrophage cytokine production and release from stimulated macrophages after modulating Fc gamma RIIIA expression. TNF-α and IL-1 α will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim 2 will focus on the mechanism

inducing cytokine production and/or release upon Fc gamma RIIIA crosslinking. Signal transduction pathways and activated transcription factors will be identified, as well as regulatory TNF-α and IL-1α promoter sequences. *Aim 3*: will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ERα and/or ERβ will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

▶ Title: *International Research Registry Network for Sjögren's Syndrome* NIDCR
P.I.: John Greenspan, Troy Daniels
Institution: University of California, San Francisco
Grant No.: N01 DE32636
Study Type: Clinical
Award: $200,000

This contract will support the creation of an International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements will include: 1) to establish a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients; 2) to collect, process, store, ship, and analyze clinical information and biological specimens from patients and families with Sjögren's syndrome; and 3) to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome.

Diabetes

▶ Title: *The Role of Inflammation and Parity on Gestational Diabetes Mellitus and Type 2 Diabetes Mellitus* NIDDK
P.I.: Wanda Nicholson, M.D.
Institution: Johns Hopkins Hospital, Baltimore, MD
Grant No.: 1 K23 DK067944-01
Study Type: Clinical
Award: $100,000

The investigator will study the role of inflammatory markers as predictors of gestational diabetes mellitus (GDM) and incident type 2 diabetes mellitus (type 2 DM), to complete advanced training in the conduct of longitudinal studies, and to transition to an independent career in clinical research. Parity has been previously linked to type 2 DM; however, the underlying mechanism for this association is unclear. Recently, markers of inflammation (e.g., C-reactive protein) have emerged as independent predictors of type 2 DM. No studies have examined whether the association of parity with type 2DM is mediated by the presence of inflammation. Moreover, it is unclear whether inflammatory markers are also predictors of GDM. The investigator proposes to determine the effect of parity and inflammatory markers on prevalent and incident cases of type 2 DM through cross-sectional and case-cohort analyses of the NHANES III and ARIC data, respectively. In addition, a prospective case-cohort study will assess inflammatory markers as risk predictors of GDM. This proposal will provide an in-depth examination of the role of parity and inflammatory markers in the pathogenesis of GDM and type 2 DM. During this award, the investigator will gain new skills and knowledge in the research methods for prospective study design, multivariate assessment of risk factors, and longitudinal data analysis. The combination of observational research, primary data collection, and advanced educational training will provide the basis for further prospective studies integrating the relation of parity and inflammation to GDM and type 2 DM. This award will give the researcher the dedicated time and experience needed to develop into an independent clinical investigator.

▶ Title: *Estrogen Effects in Insulin Target and Granulosa Cells* NIDDK
P.I.: Jerrold Olefsky, M.D.
Institution: University of California–San Diego
Grant No.: 1 R01 DK068606-01
Study Type: Basic
Award: $100,000

High fat intake is a major environmental factor leading to decreased insulin sensitivity contributing to the rising incidence of interrelated insulin resistant diseases such as Syndrome X, PCOS, type 2 diabetes mellitus, and obesity. Their investigators have demonstrated that estrogenized women and female rodents are protected from fat-induced insulin resistance, whereas, males and estrogen-deficient females are fully susceptible to these adverse effects of fat. In this application, the investigators plan a broad-based, *in vivo* and *in vitro* approach to elucidate the mechanisms of fat-induced insulin resistance and the protective effects of estrogens, using various novel animal model systems, 3T3-L1 adipocytes *in vitro*, and the non-classical insulin target tissue ovarian granulose cells (GCs). An underlying hypothesis in this application is that excess fat metabolism, due to elevated FFA levels or high fat diets, leads to activation of the "inflammatory pathway" and that specific serine/threonine kinases in this pathway, such as PKC theta, IKK beta, or JNK, or genes induced as a result of NfkappaB activation, feedback on the insulin signaling system to cause insulin resistance. Preliminary data show that treatment of 3T3-Ll adipocytes *in vitro* with FFAs leads to a marked state of cellular insulin resistance, and the investigator will exploit this novel system to conduct new studies aimed at elucidating the molecular mechanisms of FFA-induced insulin resistance and estrogen's protection against these effects. Finally, since the investigators hypothesize that GCs from insulin-resistant animals and women (particularly PCOS) can be insulin/IGF-I resistant with functional consequences, they propose an extensive series of studies in GCs prepared from normal rats and insulin-resistant rodents, to determine whether FFA treatment causes insulin resistance in these cells, as it does in insulin target cells, and to identify the underlying mechanisms. The investigators will also study the basic signaling systems for insulin, IGF-I, and FSH in these cells. Taken together, the results of these studies should greatly enhance understanding of the mechanisms of fat-induced insulin resistance, in classic and non-classic insulin target tissues, and also elucidate the mechanisms underlying the protective effects of estrogens. These studies should also highlight the role of inflammatory pathway activation in these pathophysiologic events and this may have potential therapeutic implications for new treatment approaches.

▶ Title: *Diabetes Prevention Program Outcomes Study* NIDDK
P.I.: Sarah Fowler, Ph.D.
Institution: George Washington University, Washington, DC
Grant No.: 5 U01 DK048489-11
Study Type: Clinical
Award: $300,000

While the primary goal of the Diabetes Prevention Program (DPP) was to prevent the development of diabetes, an important secondary goal was to decrease the rate of cardiovascular disease and its risk factors. These clinically important outcomes were considered as secondary during the DPP due to a lack of sufficient power in the time allotted to the study to detect potential differences between the treatment groups (ongoing analyses of the DPP data suggest that there are significant differences between the groups with regard to some cardiovascular risk factors). Following the early conclusion of the DPP, the lifestyle and metformin arms were kept on their study interventions. Due to the marked effect of lifestyle in preventing or delaying type 2 diabetes, placebo and metformin participants were also offered the same lifestyle 16-session curriculum provided to the intensive lifestyle group during what was named the 'bridge period.' The

DPP cohort being followed in the Diabetes Prevention Program Outcomes Study (DPPOS), is the largest study population with pre-diabetes, and the only population with type 2 diabetes studied from time of onset. The study cohort will provide insights regarding the clinical course of these metabolic disorders and will provide information on the persistence of the prevention or delay of type 2 diabetes. In addition, the DPP is the longest follow-up study of sustained weight loss ever conducted. Of major interest is the outcome of continued lifestyle and long-term weight loss, and metformin intervention in the gender-specific and minority sub-groups during the DPPOS.

Gastroenterology

▶ Title: *Improving Irritable Bowel Syndrome Outcomes* NINR
P.I.: Margaret M. Heitkemper, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 5 R01 NR04142-07
Study Type: Translational
Award: $100,000

In the United States, it is estimated that 10 to 20 percent of the population experience symptoms compatible with a diagnosis of irritable bowel syndrome (IBS). IBS is a functional condition characterized by change in bowel patterns (e.g., constipation, diarrhea) interfering with functional activities and increasing health care utilization. Current recommended therapies include diet manipulation, self-management, psychotherapy, and motility and pain modulation via pharmacological therapy. The primary aim of this research is to compare the distribution of SERT polymorphisms across predominate bowel pattern subgroups and gender in people with IBS. It is hypothesized that the distribution of SERT polymorphisms (5′-flanking promoter region [5-HTTLPR] and in exon2 [VNTR]) will differ across predominate bowel pattern subgroups and the distribution of SERT polymorphisms will differ by gender. Exploratory aims of this study include: 1) evaluate the relationships of SERT polymorphisms to symptom experiences and psychological profile; 2) test whether the degree of improvement in response to the CSM therapy differs by SERT polymorphism; and 3) evaluate the relationship of platelet-rich plasma 5-HT levels to SERT polymorphisms, predominate bowel pattern. This study will provide information on the potential role of serotonin processing in IBS, as well as potential gender and bowel symptom predominance. Such results may ultimately be used to tailor therapies for this common health problem.

Genitourinary

▶ Title: *Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome* NIDDK
P.I.: Sandra Berry, Ph.D.
Institution: RAND Corporation, Santa Monica, CA
Grant No.: 1 U01 DK070234-01
Study Type: Epidemiological
Award: $350,000

Interstitial cystitis (IC) is characterized by chronic and debilitating bladder pain, usually accompanied by urinary frequency and urgency. Because research has been hampered by the lack of a clear and well-accepted case definition, little is known about the prevalence of IC in the population, the full burden of disease for IC patients, the kinds of care they seek, and the kinds of treatment they receive. At present, there is no standardized questionnaire for patient screening or epidemiological studies. The lack of information about IC makes if difficult to meet patients'

needs for medical and non-medical care. Therefore, this project will establish: 1) a case definition of IC in women for patient screening or epidemiological studies using a Delphi panel of experts in IC and diseases with similar symptoms; 2) develop and validate a symptom questionnaire that can be used to identify female IC patients and distinguish them from those with similar conditions (e.g., overactive bladder, urinary tract infection, and endometriosis); 3) develop an IC-specific measure of self-reported functional status, including physical, mental, social, sexual/relationship, role functioning, and other factors identified by IC patients as important; 4) survey more than 300,000 women for urinary symptoms and, using the validated symptom questionnaire, screen more than 23,000 to estimate prevalence of IC in the United States and provide a sample of 354 women over age 18 who fit the case definition for IC and 300 who have IC-like symptoms; and 5) describe the impact of IC on patient's lives, including IC-specific functional status and the impact of IC on quality of life, mental and physical health, stress and coping, social support, sexual functioning, social functioning, labor force participation and income, as well as utilization of traditional and alternative care and compare these results with existing data on disease burden for other chronic diseases.

▶ Title: *Risk Factors for Decline in Renal Function* NIDDK
P.I.: Gary Curhan, M.D.
Institution: Channing Laboratory, Boston, MA
Grant No.: 1 R01 DK066574-01A1
Study Type: Clinical
Award: $100,000

Renal failure is a life-threatening and costly medical condition. End-stage renal disease, defined as severe renal dysfunction requiring chronic dialysis or kidney transplantation, is increasing in prevalence and has an annual mortality rate exceeding 20 percent. Less severe loss of renal function also has important health consequences. Mild to moderate reductions in renal function and microalbuminuria are important predictors of cardiovascular disease and death, in high-risk groups as well as in the general population. The risk of adverse outcomes increases with decreasing renal function. Even in the absence of known risk factors for renal function decline, such as hypertension or diabetes, kidney dysfunction may develop slowly over decades. Slowing or preventing decline in renal function may favorably impact morbidity and mortality. Genetic factors, biological processes (such as inflammation), and environmental factors (such as analgesic use), may contribute to renal function decline. Heightened activity of the renin-angiotensin system (RAS), particularly of angiotensin II, is an important mediator of renal pathophysiology. Thus, genes related to the RAS system may have important long-term effects on renal function. Chronic inflammation may adversely affect the kidney by causing vascular disease and fibrosis. Analgesics are the most commonly used drugs in the United States, and chronic analgesic use may be an important, preventable cause of renal dysfunction. The primary objective of this study is to examine prospective risk factors for renal function decline, defined as decline in estimated glomerular filtration rate (using serum creatinine) and development of microalbuminuria, among 5,000 participants in two large female cohorts: the Nurses' Health Study I (NHS I) and the Nurses' Health Study II (NHS II). Stored and newly collected blood and urine specimens will permit repeated measurements of renal function and urine albumin and will allow us to examine changes over a period of 19 years in NHS I and 11 years in NHS II. Mixed-effects regression will be used to analyze the slope of renal function in the exposed and unexposed groups during the long-term followup. This study will provide: 1) prospective data on risk factors for renal function decline; 2) threshold levels of safe cumulative dose of individual classes of analgesics; 3) population-based incidence rates of renal dysfunction and rate of renal function decline in younger and older women; and 4) an important resource for future long-term studies of renal function decline.

▶ Title: *The Function of the Urethera in Continent Women* NICHD
P.I.: Kimberly Kenton, M.D.
Institution: Loyola University of Chicago, IL
Grant No.: 1 K23 HD047325-01A1
Study Type: Clinical
Award: $97,054

This application requests funds for two purposes: career development and research. The applicant plans to obtain a Master of Science in Clinical Research Design and Statistical Analysis from the University of Michigan. Short-term goals include the obtaining the Master's degree and beginning an innovative well-designed patient-oriented research project under the mentorship of a highly productive clinical researcher. The long-term goals include developing into an independent patient-oriented researcher with expertise in electrodiagnosis and urethral function, enhancing research abilities with a better understanding of methodology and designing follow-up studies to prevent and treat neuromuscular injuries to the urethral sphincter, submission of an RO1 to fund such studies, and developing research mentoring skills to begin training the next generation of patient-oriented clinical researchers. The specific aims of the research plan are: 1) to acquire high-quality neuromuscular signals from the urethra using concentric needle EMG (with quantitative motor unit analysis) and current perception threshold testing to test the null hypothesis that there are no differences in urethral neuromuscular function in: a) Caucasian and African American women; b) continent and stress incontinent women; and c) continent nulliparous and parous women. 2) To establish quantitative parameters of urethral sphincter function in women of various races. Normative ranges will be calculated for EMG, current perception thresholds, and urethral pressures for Caucasian and African American women. These data can then be used by other centers as reference data.

▶ Title: *Weight Reduction for Incontinence Network (WIN)* NIDDK
P.I.: Deborah G. Grady, M.D., (Rena Wing, Ph.D., Frank Franklin, Ph.D.)
Institution: University of California–San Francisco; Miriam Hospital, Providence, RI; and University of Alabama–Birmingham
Grant No.: 5 U01 DK67860-02, DK067861-02, DK067862-02
Study Type: Clinical
Award: $250,000

Urinary incontinence is a common problem among women that causes distress, diminished quality of life, and dramatic limitations in daily functioning. Overweight women are at significantly increased risk of urinary incontinence; over 65 percent of women with incontinence are overweight. Data from short-term, preliminary studies suggest that weight reduction may significantly reduce incontinence episodes. Thus, weight loss may present a promising new approach to urinary incontinence, one likely to produce a cascade of broader health improvements in addition to reductions in frequency of urinary incontinence. Therefore, we propose to randomize 330 overweight and obese women with urinary incontinence (165 at each of two clinical centers) to a 6-month intensive behavioral weight control program or to usual care to determine the short-term effect of weight loss on frequency of incontinence and quality of life, to identify women most likely to benefit from weight loss, and to begin to explore the urodynamic mechanisms underlying incontinence improvement following weight loss.

HIV/AIDS

▶ Title: *Impact of Delivery Models in HIV Health Care* FIC
P.I.: Ximena L. Burbano, M.D.
Institution: Fundacion Santa, Bogota, Columbia
Grant No.: 5 R01 TW006218-02
Study Type: Clinical
Award: $20,000

Colombia, which ranks fourth in the total number of HIV reported cases in Latin America, has designed different Delivery Health Care Models to provide coverage for HIV-infected patients. The proposed health research initiative, by a new foreign investigator, will evaluate for the first time, the utilization and cost implications of different representative delivery health care models in Bogota, Colombia. Assessment of cost effectiveness is vital not only in the area of treatment but also in regard to the use of diagnostics, provision of care, support services, and prevention strategies and programs. A multi-step evaluation of three main Delivery Health Care Models (Open Pre-Paid, EPS, Social Security) available in Bogota, will be undertaken. First, information will be obtained to determine the type of specific services available for each delivery model. Second, data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase, models will be compared in terms of health services utilization, costs, cost effectiveness, and which health care model best accomplishes delivery and sustains adherence to HAART. Evaluation of service utilization will consider the impact on disease progression, as indicated by CD4 cell count and viral burden. Outcomes will be aggregated to determine the level of total services required for adequate care for each delivery model. Findings from this project should provide necessary information to help determine the optimal use of HIV delivery services and help develop public health strategies to achieve equity in health services, for HIV-infected people in Colombia, and possibly other countries in Latin America.

▶ Title: *Interventions to Reduce HIV-1 Incidence after Delivery* FIC
P.I.: James N. Kiarie, M.D.
Institution: University of Nairobi, Kenya, Africa
Grant No.: 5 R01 TW006640-02
Study Type: Clinical
Award: $20,000

Women in sub-Saharan Africa face a high risk of HIV-1 acquisition during the first year postpartum which can be reduced by antenatal voluntary counseling and testing (VCT) and using female controlled HIV-1 prevention methods. In preventing heterosexual HIV-1 transmission, the success of female-controlled methods such as female condoms, the vaginal diaphragm, and vaginal microbicides depends on their use by women at a high risk of HIV-1 infection. In studies of prevention of mother-to-child transmission, little attention has been paid to women identified as HIV-1-negative and their risk of becoming infected after delivery. An understanding of the factors that influence HIV-1 incidence among uninfected mothers, and which female-controlled prevention methods are most acceptable to them, is crucial for preventing HIV-1 acquisition in these women, and hence, preventing additional mother-to-child transmission of HIV-1 in future pregnancies. This study proposes to determine the potential effectiveness of female-controlled HIV-1 prevention methods, and the impact of participation in perinatal HIV-1 prevention programs on HIV-1 incidence in the first year after delivery (assessed using a detuned ELISA at 9 to 12 months postpartum) in three sites in Kenya. The specific aims of the study are to: 1) determine the correlates of incident of HIV-1 infection among Kenyan women in the first year postpartum; 2) compare the incidence of HIV-1 infection among women who have participated in perinatal

HIV-1 prevention programs to the incidence among those who have not participated in these programs; 3) determine women's knowledge, attitudes, and willingness to use vaginal microbicides, the female diaphragm, and female condoms; and 4) estimate the effectiveness of the various HIV-1 prevention methods based on theoretical efficacy, the number and HIV-1 infection risk of women willing to utilize these methods. This study will provide important information on how to increase the effectiveness of female-controlled HIV-1 prevention methods by targeting women at a high risk of acquiring HIV-1 infection. The study will also identify ways to increase the impact of antenatal VCT in reducing HIV-1 incidence.

▶ Title: *AIDS International Training and Research Program* FIC
P.I.: Arthur L. Reingold, M.D.
Institution: University of California, School of Public Health, Berkeley
Grant No.: 3 D43 TW000003-05
Study Type: Clinical
Award: $50,000

The University of California, San Francisco–Gladstone Institute of Virology & Immunology Center for AIDS Research (UCSF-G1VI CFAR) will collaborate with the University of California, Berkeley's (UCB) Fogarty AIDS International Training and Research Program (AITRP) providing support for competitive training grants. Training grants will be led by CFAR members in collaboration with in-country collaborations in five resource-limited settings selected for the scale and stability of ongoing international HIV research. Training will focus on scientists from countries and projects integral to the UCB/UCSF AITRP. Training will be provided in country or in San Francisco and will take advantage of CFAR member expertise and CFAR Scientific Core capabilities. Training projects will be selected in a competitive mentored process after a publicly announced request for training proposals. Letters of intent responsive to the UCSF-GIVI focus on enhancing cross-disciplinary translational research will be invited to submit full, but brief, proposals linking training needs in-country with ongoing research projects. Proposals will be reviewed by an expert peer panel with final funding decisions made by the UCSF-G1VI CFAR co-directors. Effectiveness of training will be monitored and assessed by written progress reports and evidence of subsequent research grant funding and publications. To accomplish this goal, the following aims will be addressed: 1) evaluate the training needs at each of the five CFAR international sites; 2) support investigators from one or more priority sites in training at the UCSF-GIVI CFAR, and /or; 3) support UCSF-GIVI investigators to provide training at one or more priority sites(s); 4) provide access to UCSF-GIVI CFAR' core laboratories and other resources for UCB/UCSF AITRP priority site investigators in pilot research projects; and 5) monitor and evaluate the success of research training support at priority sites as evidenced by important research grants, publications, and/or findings.

▶ Title: *Scale-up of Community-based HIV Prevention and Care* FIC
P.I.: Warren D. Johnson, M.D.
Institution: Well Medical College of Cornell University, Department of Medicine, New York, NY
Grant No.: 3 D43 TW000018-16S5
Study Type: Clinical
Award: $50,000

This proposal requests support for the Harvard University Program in Infectious Disease and Social Change/Partners in Health/Zanmi Lasante to continue training Haitian scientists in the performance of biomedical, epidemiological, and biosocial research in the programmatic implementation of HIV prevention and treatment and the care of individual patients with HIV in rural Haiti. The program is based at Clinique Bon Saveur in Change, Haiti, with responsibility for the provision of healthcare services for the population of the Central Plateau. The principal

investigator is Paul Farmer, M.D., Ph.D., who is based at Harvard Medical School in the Program in Infectious Disease and Social Change. The training team has many years of experience in HIV prevention and treatment in rural Haiti, including the prevention of mother-to-child transmission, diagnosis, and treatment of TB and sexually transmitted disease, the prevention of opportunistic infections, and the use of highly active antiretroviral therapy. The principal investigator of the AITRP grant, Dr. Warren Johnson, is a long-standing supporter of the work done in Change and the Central Plateau, and this collaborative training program has been highly successful. The program will continue to emphasize long-term training and advanced research training in Haiti. Because HIV does not exist as a separate entity, the approach at PIH/ZL is to integrate the prevention and treatment of HIV with the most vulnerable and high prevalence groups that are seen at Clinique Bon Saveur. HIV-related services include: 1) HIV prevention and treatment, including expansion of access to voluntary counseling and testing (VCT); 2) the screening and treatment of STIs; 3) the prevention of mother-to-child transmission; and 4) TB case detection, treatment, and VCT (approximately 50 percent of HIV patients in the Central Plateau present with TB). These four activities are referred to by PIH/ZL as the "four pillars" of HIV control. The overall program goal of this grant is to provide training that will increase local capacity to perform research on service integration, diagnosis, and treatment of HIV in central Haiti within these four pillars of HIV control. Long-term benefits will include the increases in research capacity for future HIV-related research activities in Haiti.

▶ Title: *AIDS International Training and Research Program* FIC
P.I.: King K. Holmes, M.D., Ph.D.
Institution: University of Washington, College of Medicine, Seattle
Grant No.: 5 D43 TW000007-17
Study Type: Clinical
Award: $50,000

This program proposes to develop a fifth AIDS International Training and Research Program (AITRP) site in New Delhi at the All India Institute of Medical Sciences (AIIMS) to address the growing HIV epidemic in India. Other target countries have been Kenya, Peru, Mozambique, and Thailand. The University of Washington (UW) AITRP selected AIIMS as the site for program expansion for several reasons. First, AIIMS is a premier institution for biomedical research and training in India, and successful collaborative research is already being performed between scientists at the UW (Uma Malhotra and Julie McElrath) and AIIMS (Pradeep Seth and Madhu Vajpayee) within the framework of an existing longitudinal cohort of HIV-1-infected subjects at AIIMS. Second, UW International Training and Research in Emerging Infectious Diseases (ITREID) has a site in New Delhi and the two programs will collaborate in their research and training efforts in the region. The IATRP program direction and the core/resource faculty will be identical to that described for the parent program. The overall goal of this proposal is to develop a center for excellence in HIV-1 research in India with independent and sustainable research capacities in the prevention and control of HIV. A number of training needs and research priorities have been identified and include: 1) strengthening of the infrastructure for field research through training and capacity building in the area, 2) development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, and 3) strengthening the immunology research program through training of laboratory scientists in state-of-the-art immunology assays. The site will emphasize training in the Epidemiology Track and the Laboratory Track and will focus on long- and medium-term training. Recruitment of scientists into the Laboratory Track will occur in the Department of Microbiology. Recruitment efforts for trainees interested in the Epidemiology Track will take place in the Department of Community Medicine in collaboration with the Head of the AIDS Education and Training Program in New Delhi. Collaborative research and training during the first year will emphasize: 1) seroprevalence

and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, 2) clinical profile of HIV-1 clade C infection in India, 3) cellular immunity to HIV-1 clade C viruses and diversity consideration in vaccine development, and 4) HIV-1 shedding and mucosal immunity. The existing longitudinal patient cohort will provide a foundation for new cohorts and continued collaborative research. Through these endeavors in multidisciplinary research and training, it is anticipated that the program will facilitate the establishment of critical expertise in biomedical and prevention research at the AIIMS to combat the growing HIV-1 epidemic in the region.

Immunity/Autoimmunity

▶ Title: *Innate and Adaptive Regulatory T Cells in Immune Tolerization of Rheumatoid Arthritis* NIAID
P.I.: Salvatore Albani, M.D., Ph.D.
Institution: University of California–San Diego
Grant No.: 1 R21 AI059957-01
Study Type: Clinical
Award: $230,375

It has been suggested that two categories of innate and adaptive regulatory T cells (Treg) can be identified by phenotypical and functional characteristics. "Innate" and "adaptive" Treg would cooperate in limiting potentially noxious inflammatory processes. This regulatory function may be impaired in autoimmunity. Its restoration could provide novel therapeutic approaches. This project aims to unravel the role which may pertain to Treg function in induction of tolerance to an antigenic peptide (dnaJP1) in rheumatoid arthritis (RA). One hundred and five samples from RA patients treated in the context of a Phase I (completed) and a Phase II (ongoing) clinical trial with dnaJP1 or placebo have already been collected at the beginning of treatment and at monthly intervals. The investigators will test whether mucosal tolerization to a peptide is associated with emergence of cells with a regulatory phenotype. They will also determine if a proportion of Treg are dnaJP1-specific, and if numbers and functional characteristics of these cells change as a consequence of immunotherapy. The specific aims are: *Specific Aim 1*–To characterize "innate" and "adaptive" Treg in serial samples obtained from a tolerization trial in rheumatoid arthritis and to explore their functional role in the tolerization process. SA1a–Peripheral blood mononuclear cells (PBMC), synovial fluid mononuclear cells (SFMC), and T cells obtained from synovial membranes of RA patients will be evaluated by FACS analysis for phenotypical markers characteristic of T regulatory T cells. In particular, levels of CD25, CD4, CTLA4, and CCR4 will be studied. "Innate" and "adaptive" T cells will be differentiated based an a set of phenotypical and functional variables, including levels of CD25 expression and quantification on sorted cells by real time polymerase chain reaction (TaqMan) gene expression of several molecules putatively involved in Treg function. These genes will include IL-10, TGF beta, IL-4, FOXP3, and CTLA. Samples obtained will be also tested in *in vitro* studies to explore regulatory properties of "innate" and "adaptive" Treg on T cell responses to recall antigens, as well as to antigens (gp39, dnaJPl, and p205) putatively involved in the pathogenic process. *Specific Aim 1b*–Clinical information will be compared with immunological data. *Specific Aim 2*–To investigate whether some Treg have specificity for dnaJpl and whether functional and phenotypical characteristics of dnaJP1-specific Treg are associated with the course of the tolerization process. Functional characteristics of sorted cells will be evaluated by TaqMan.

▶ Title: *Mitochondrial Dysfunction in Patients with Systemic Lupus Erythematosus* NIAID
P.I.: Andras, Perl, M.D., Ph.D.
Institution: SUNY Upstate Medical University, Syracuse, NY
Grant No.: 1 R01 AI061066-01
Study Type: Basic, clinical
Award: $152,000

Abnormal T-cell activation and cell death underlie the pathology of systemic lupus erythematosus (SLE). Immune responses resulting in activation, proliferation, or programmed cell death are dependent on controlled production of reactive oxygen intermediates (ROl) and ATP in mitochondria. In turn, synthesis of ATP and containment of cell death-inducing factors within the mitochondria are dependent on the mitochondrial transmembrane potent which is subject to regulation by oxidation-reduction equilibrium of ROI, pyridine nucleotides (NADH/NAD + NADPH/NADP), and GSH levels. Mitochondrial hyperpolarization and transient ATP depletion have been identified in the investigators laboratory as early and reversible steps in normal T-cell activation and apoptosis. By contrast, T lymphocytes of patients with SLE exhibit persistent mitochondrial hyperpolarization, cytoplasmic alkalinization, and increased ROT production, as well as diminished levels of intracellular glutathione and ATP. Oxidative stress affects expression and signaling through the T-cell receptor, cell death receptors, and CD38, as well as activity of redox-sensitive caspases and transcription factors mediating lymphokine production. Mitochondrial dysfunction leading to ATP depletion may be ultimately responsible for diminished activation-induced apoptosis and sensitize lupus T cells to necrosis. The investigators recently discovered that T-cell activation-induced mitochondrial hyperpolarization is mediated by Ca2+- and ROI-dependent production of nitric oxide (NO). This proposal is focused on understanding the mechanism of persistent mitochondrial hyperpolarization in lupus T cells. *Specific Aim 1*–Further characterize the role of mitochondrial signal processing, with an emphasis on production of NO and ROI, cytoplasmic alkalinization, and Ca fluxes with respect to aberrant T cell activation and cell death in patients with lupus and healthy and rheumatoid arthritis controls. *Specific Aim 2*–Assess functioning of isolated mitochondria and metabolic pathways connected to regulation, production, and synthesis of ATP and pyridine nucleotides. *Specific Aim 3*–Assess coordinate changes in gene expression involved in T-cell activation, apoptosis, and metabolism to delineate pathways contributing to or affected by mitochondrial hyperpolarization in SLE. *Specific Aim 4*–Systematically validate signaling pathways located upstream and downstream of mitochondrial hyperpolarization and identify signals capable of normalizing mitochondrial dysfunction in lupus T cells. Thus, checkpoints of mitochondrial hyperpolarization could represent novel targets of pharmacological intervention in patients with SLE.

▶ Title: *Sex-based Differences in Anti-viral Immunity and Systemic Lupus Erythematosus* NIAID
P.I.: Sally R. Sarawar, Ph.D.
Institution: LaJolla Institute, San Diego, CA
Grant No.: 5 R21 AI51862-04
Study Type: Basic
Award: $50,000

Systemic lupus erythematosus (SLE) is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses, has been reported. However, some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic

loci that control disease susceptibility in these mice has been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci designated SLE 1, 2, and 3 have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gamma herpes virus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus with MHV-68, can induce or exacerbate autoimmune disease, and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection and whether their expression correlates with the induction of autoimmune disease.

▶ Title: *Mechanism Regulating Neutrophil Activation in Pregnancy* NIAID
P.I.: Howard R. Petty, Ph.D.
Institution: Wayne State University, Detroit, MI
Grant No.: 5 R01 AI51789-04
Study Type: Translational
Award: $50,000

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic, as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis), as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study offers a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

▶ Title: *Sex-based Differences in the Immune Response* NIAID
P.I.: Betty Diamond, M.D.
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 5 R01 AI51767-03
Study Type: Basic
Award: $50,000

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and B cell activation, and to understand what underlies an estrogen mediated breakdown in humoral self tolerance. The three Specific Aims are: *Aim 1*: investigates the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B-cell repertoire selection. *Aim 2*: addresses the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on

how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in Pyk-2-deficient mice. *Aim 3*: characterize estradiol-induced signaling pathways that may alter B-cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of sexual dimorphism in this phenomenon.

▶ Title: *Predictors of Pregnancy Outcome in Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome* NIAMS
P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 5 R01 AR049772-02
Study Type: Clinical
Award: $400,000

Thrombosis and pregnancy loss are common features of systemic lupus erythematosus (SLE), particularly in the presence of antiphospholipid (aPL) antibodies. The *in vivo* mechanisms by which aPL antibodies lead to vascular events and, specifically, to recurrent fetal loss are largely unknown. Our studies in a murine model of antiphospholipid antibody syndrome (APS) indicate that *in vivo* complement activation is necessary for fetal loss caused by aPL antibodies. This proposal represents a first-time effort to translate novel research observations on the potential role of complement activation in the pathogenesis of aPL antibody-mediated pregnancy loss to a clinically relevant human study. No study has investigated whether complement is activated in patients with aPL-associated poor pregnancy outcomes (with or without SLE), and whether particular patterns of complement activation characterize and thus can distinguish these patients from SLE patients without aPL-antibodies or fetal loss, and from patients with normal pregnancy. Preliminary data in murine APS, the availability of more accurate tests of complement activation, and the recent development of effective and specific complement inhibitors argue persuasively that the role of complement in aPL-associated pregnancy complications should now be examined. Accordingly, the specific aim of the study is: To determine whether elevations of split products generated by activation of the alternative or classical complement pathways predict poor fetal outcome in patients with antiphospholipid antibodies and/or SLE. The investigators propose a prospective observational study of over 400 pregnant patients, enrolled at six major clinical centers, and grouped and analyzed according to the presence or absence of aPL and pre-existing SLE. A core group of investigators with recognized expertise in SLE and aPL pregnancy, high-risk obstetrics, the basic biology of complement, and statistical methods in SLE studies have been assembled. Detailed medical and obstetrical information during the course of pregnancy and serial blood specimens for complement and cytokine assays will be obtained, and analyzed to identify predictors of poor fetal outcome. Placentas will be studied to characterize tissue pathology and mediators of injury. RNA, DNA, serum, and urine will be stored for studies to elucidate temporal changes in gene expression during the course of complicated and uncomplicated pregnancies and to investigate genetic polymorphisms. The investigators hypothesize that this study will provide insights into the mechanisms of complement-mediated inflammatory disorders and suggest means to prevent, arrest, or modify these conditions. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable the investigators to initiate an interventional trial of complement inhibition in patients at risk for aPL antibody-associated fetal loss. The identification of such surrogate markers in aPL and SLE patients may also prove generally applicable to anticipate complications during pregnancy in disease-free women.

▶ Title: *Brain Connections* NIAMS
P.I.: Michelle A. Petri, M.D.
Institution: John Hopkins University, Baltimore, MD
Grant No.: 5 R01 AR49125-03
Study Type: Clinical
Award: $80,000

Neuropsychiatric manifestations of systemic lupus erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of co-morbidities or ethnicity/race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE from ten sites will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines, and adhesion molecules), and co-morbidities (race/ethnicity, depression, fibromyalgia, and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

▶ Title: *Identifying Genes for Neuropsychiatric Lupus* NIAMS
P.I.: Nilamadhab Mishra, M.D.
Institution: Wake Forest University, Winston-Salem, NC
Grant No.: 5 R21 AR49153-03
Study Type: Basic
Award: $40,000

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of systemic lupus erythematosus (SLE) by microarray analysis. SLE is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity and mortality. It is a multisystern rheumatic disease with a wide variety of associated clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system function. Although the gene responsible for neurological disturbances in SLE is not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine gene expression in hippocampus and cerebellum are responsible for the neurological deficit.

▶ Title: *Antibodies to NR2 in Systemic Lupus Erythematosus* NIAMS
P.I.: Betty Diamond, M.D.
Institution: Yeshiva University, New York, NY
Grant No.: 5 R01 AR49126-03
Study Type: Clinical
Award: $60,000

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with systemic lupus erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF) as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists and whether there is T-cell recognition of NR2 epitopes. Also, rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

▶ Title: *Brain Cell Death in MRL Mice: Targets and Mechanisms* NIAMS
P.I.: Boris Sakic, Ph.D.
Institution: McMaster University, Ontario, Canada
Grant No.: 5 R21 AR49163-03
Study Type: Basic
Award: $20,000

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MIRL-Ipr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, cerebrospinal fluid (CSF) neurotoxicity, and an anxiety/depressive behavioral state in MRL-Ipr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1) whether DNA fragmentation involves neurons, glial, and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining); 2) whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSIF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-Ipr mice); 3) whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology with electron microscopy, by detecting DNA laddering with chemilumnescent method and caspase activation with immunohistochemistry); and 4) whether immunosuppression prevents neurodegeneration and CSF neurotoxocity.

▶ Title: *Virginia Mason/UCHSC Autoimmune Center* NIAID
P.I.: George S. Eisenbarth, M.D.
Institution: University of Colorado, Denver
Grant No.: 5 U19 AI50864-04
Study Type: Translational
Award: $200,000

This grant consists of three research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic,

immunologic, and environmental determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T-cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for rheumatoid arthritis and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. Project 3 will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

▶ Title: *How Does Blockage of CD40/CD40L Prevent Autoimmunity?* NIAID
P.I.: Matthias Von Herrath, M.D.
Institution: Scripps Research Institute, La Jolla, CA
Grant No.: 5 U19 AI51973-04
Study Type: Basic, animal models
Award: $100,000

All three projects of the consortium application are targeted at better understanding induction of long-term tolerance by costimulation blockade of CD40/CD40L interactions with a CD40L antibody. The investigators believe that this immune-based intervention is one of the most promising and attractive approaches currently in clinical trials for several autoimmune disorders. Many of these ongoing interventions (psoriasis, transplantation, etc.) show much promise and only one trial had to be stopped due to deleterious side effects (enhanced blood clotting), which was likely caused by the antibody preparation or too high dosages, since it did not occur in other clinical studies. Although it is known that CD40-CD40L interactions are required for dendritic cell maturation and activation, as well as generation of effector lymphocytes, many mechanistic issues remain unresolved. The most crucial of these will be addressed by the three projects united in the present U-19. Effects on lymphocyte differentiation and effector functions (Sarvetnick), T cell proliferation, differentiation and APC-trafficking (Miller), and induction of regulatory APCs or lymphocytes able to downmodulate aggressive autoimmune responses antigen specifically (von Herrath) will be studied by the single components. In addition to analyzing differential effector mechanisms, three distinct models for autoimmune diseases will be utilized (Sarvetnick, NOD; Miller, EAE; von Herrath, RIP-LCMV). This multi-focal approach will result in a more rapid and thorough understanding of a CD40L-induced immune modulation and/or suppression. Furthermore, paradigms or discoveries applicable to a human situation should ideally be validated and tested in various animal models. Therefore, the direct comparison of three autoimmune models will enable us to define which *in vivo* consequences of co-stimulation blockade occur more commonly and which are restricted to a given experimental situation.

▶ Title: *Fine Specificity of Scleroderma Autoantibodies* NIAMS
P.I.: Judith James, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 5 R01 AR48045-04
Study Type: Translational
Award: $200,000

Systemic sclerosis (scleroderma) is a disfiguring, multisystem disease of unknown etiology, which is characterized by a broad spectrum of disease manifestations with varying organ involvement. Raynaud's phenomenon, the dysregulated vascular contraction of the terminal arteries of the circulatory system, is present in almost every case. Vascular insufficiency in these patients is associated with a vasculopathy causing tissue ischemia, which is directly linked to progressive fibrosis of specific target organs, such as the skin, lung, heart, gastrointestinal tract, and kidney. Although the underlying pathophysiology of this disorder remains an enigma, the presence of anti-nuclear antibodies in scleroderma patients is nearly universal. Targets of these autoantibodies include

topoisomerase 1 (Scl-70), nuclear ribonucleoproteins (nRNP), centromere, PM-Scl, and Ku. Anti-topoisomerase-1 (topo to 1) autoantibodies are quite specific for scleroderma, and are present in precipitating levels in 20 to 40 percent of patients. Anti-topo 1 is associated with diffuse skin thickening, lung involvement, and the development of lung, colon, and brain cancer. Scleroderma patients with anti-nRNP autoantibodies may have a more cutaneous form of the disease and universally suffer from Raynaud's phenomenon. Over the past decade the immunochemistry of lupus autoantigens have been extensively characterized. These previous studies provide the technical background for this proposal. Epitope mapping experiments of the lupus spliceosomal autoantigens have led to a peptide-induced model of lupus autoimmunity. These studies have identified a potential etiological trigger and pathogenic mechanisms. These well-honed techniques will be applied, as well as a similar scientific strategy, to analyze the humoral fine specificity of the anti-nRNP and anti-topoisomerase autoantibodies found in scleroderma. Preliminary data suggest a dramatic difference in the anti-nRNP response of SLE patients and scleroderma patients with nRNP autoantibodies. This project seeks to identify the common humoral epitopes of nRNP and topoisomerase-1 in scleroderma and primary Raynaud's, to describe the development of these humoral autoimmune responses over time (and with therapy), to establish potential etiological triggers of these rheumatic diseases, and to understand the role of these specific autoantibodies in scleroderma disease pathogenesis.

▶ Title: *Studies of Collagen Gene Regulation in Two Murine Models* NIAMS
P.I.: Stephen H. Clark, Ph.D.
Institution: University of Connecticut, Farmington
Grant No.: 5 R01 AR48082-04
Study Type: Basic, animal models
Award: $200,000

This proposal will utilize two mouse mutations that are models for scleroderma, tight skin (Tsk), and tight skin 2 (Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark feature of the human disease. The long-range objective of the proposed research is to utilize these two mutations, combined with several lines of transgenic mice, as experimental tools to dissect molecular mechanisms of disease pathogenesis. Specific experiments are proposed for the identification of genes involved in the regulation of extracellular matrix synthesis in dermal fibroblasts. Two experimental strategies are planned and are encompassed in three specific aims. *Specific Aim 1* focuses on identifying cis-acting elements in the type I collagen gene required for the increased production of Collal mRNA in mutant dermal fibroblasts. Defining "fibrotic" specific elements will provide a basis for the identification of the transacting factors that interact with these DNA segments to increase Collagen gene expression. These elements will be defined by studying the expression of Collal CAT reporter transgenes bearing various segments of the 5′ promoter region, as well as specific deletions of the first intron. The expression of each transgene will be evaluated in skin samples isolated from Tsk, Tsk2, and normal mice. Also, transgene expression will be measured in dermal fibroblasts cultured from skin explants isolated from these mice. To generate experimental mice, Tsk and Tsk2 mutant mice will be crossed with transgenic mice bearing the various collagen transgene constructs. A potential role of the Collal first intron in the upregulation of transcription of the Collal gene has been shown with the Tsk and Tsk2 mutations (our preliminary data), as well as in scleroderma dermal fibroblasts. In *Specific Aim 2*, the role of the Collal first intron in regulating transcription of the Collal gene and the development of the Tsk and Tsk2 fibrotic skin phenotype will be determined. For these experiments a targeted deletion in the Collal first intron will be employed. This experimental model has a unique feature permitting the determination of the levels of Co11a1 mRNA

produced by the deleted and normal allele in the same RNA preparation. Further, this genetic system allows the monitoring of gene expression in the context of the endogenous gene. A second experimental direction involves identifying genes in dermal fibroblasts that are associated with elevated levels of collagen production employing micorarray analysis. The experimental plan outlined in *Specific Aim 3* includes the development of reagents to isolate specific populations of dermal fibroblasts cultured from both mutant and normal animals based on their collagen gene expression. This will be accomplished by employing a collagen promoter GFP reporter transgene that has been documented to display elevated expression in dermal fibroblasts isolated from both Tsk and Tsk2 mutant mice. Flow cytometric analysis of dermal fibroblasts expressing this transgene will permit the isolation of cell populations based on their level of collagen expression. RNAs will be extracted from high-collagen- and low-collagen-producing cell populations. These RNAs will be utilized in a microarray analysis to identify genes differentially expressed in high-collagen-producing cells compared to low-collagen-producing cells and visa versa. It is anticipated that genes identified in this experimental paradigm will permit the dissection of molecular pathways that are involved with the onset of scleroderma and potentially lead to therapies to control extracellular matrix metabolism.

▶ Title: *Epstein-Barr Virus Nuclear Antigen-1 in Lupus* NIAID
P.I.: John B. Harley, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 5 R01 AI31584-11
Study Type: Basic
Award: $200,000

The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. The investigators believe that novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus nuclear antigen-l (EBNAl), which contains a peptide sequence that inhibits antigen presentation and class I HLA-dependent cytotoxic T-cell responses. Preliminary data show that EBNA-l also contains sequences that appear to be differentially bound by SLE as opposed to normal sera. We propose to study SLE from the perspectives of the anti-EBNA-l humoral immune response, of EBNA-l expression in B cells, and of EBNA-l sequence variants. We plan to use the early-immediate antigen-l (El-l) of cytomegalovirus (CMV) as a control antigen. This project is a research for AI 31584 for year 09. Work in the current funding period is focused upon serology before diagnosis of SLE, made possible by over 20,000,000 sera in the Army Navy Serum Bank. The results to date from the first 130 SLE patients and 520 controls have established that autoimmune serological changes are present years before clinical manifestations and that autoantibody specificities vary greatly with regard to their temporal relationship to illness. Because of the high EBV infection rate among women and African American men, the temporal relationship between EBV infection and SLE could not be tested. The final aim of this competitive renewal is to continue accruing the appropriate military cases and controls to provide sufficient power to test the hypotheses that EBV infection precedes clinical onset of SLE and that anti-EBNA-l precedes the onset of lupus autoantibodies. Establishing the role of ubiquitous agents, such as EBV, in chronic disease is especially difficult. In this situation, specific associations of SLE with immune response variations, with viral gene product expression, and with viral variants will be sought in an effort to explore particular mechanisms of pathogenesis as a strategy to more convincingly implicate EBV in the etiology of SLE.

▶ Title: *Registry and Repository of African Americans with Rheumatoid Arthritis* NIAMS
P.I.: Larry Moreland, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 1 N01 AR002247-000
Study Type: Clinical
Award: $200,000

This 5-year project will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (RA) and establish a registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast United States will gather data, which will provide a resource for investigators interested in the genetics of RA in AA. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor-α [TNF-α]/lymphotoxin (LT)-α, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3-years disease duration in AA.

▶ Title: *UCSF Autoimmunity Center of Excellence* NIAID
P.I.: David Wofsy, M.D.
Institution: University of California–San Francisco
Grant No.: 5 U19 Ai056388-02
Study Type: Clinical
Award: $60,000

The broad aim of this application is to translate advances in immunology and molecular biology into practical, safe, and effective therapies for people with autoimmune diseases. Toward this end, the investigators will participate in collaborative clinical trials of novel immunotherapies, and we will conduct basic research into the mechanisms that lead to autoimmunity, as well as the mechanisms that can be harnessed to prevent autoimmunity. This proposal to become an Autoimmunity Center of Excellence consists of a Clinical Center, two basic research projects, and an Immune Function Monitoring Core. Clinical Center investigators involved in this application have extensive experience in the conduct of clinical trials in diverse autoimmune diseases. This application focuses primarily on systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type I diabetes mellitus (IDDM). Two clinical protocols are proposed, both based on basic research conducted at UCSF by participants in this proposal. Protocol 1 is based on the observation that blockade of T cell co-stimulation by CTLA4Ig, in combination with conventional therapy with cyclophosphamide, produces long-lasting benefit in murine lupus. It tests the hypothesis that this approach to therapy will be effective in people with lupus nephritis. Protocol 2 is based on the observation that HMG-CoA inhibitors (statins) retard murine models for MS. It tests the hypothesis that atorvastatin will prevent progression to MS in patients at high risk.

▶ Title: *Treatment of Autoimmune Disease by Co-stimulatory Signal* NIAID
P.I.: Samia J. Khoury, M.D.
Institution: Brigham and Women's Hospital, Boston, MA
Grant No.: 5 U19 AI046130-06
Study Type: Clinical
Award: $60,000

There have been tremendous advances in the field of autoimmunity in the last 20 years, and our understanding of the mechanisms underlying autoimmune disease has grown exponentially. True tolerance is likely to arise not from improved immunosuppression, but from improved understanding of the normal mechanisms that generate and maintain self-tolerance, and the ability to

manipulate these mechanisms for the prevention and treatment of autoimmune diseases. The mechanisms of autoimmunity that underlie many diseases are similar, and an integrated multi-specialty approach for evaluating new and emerging therapies would provide the opportunity to integrate knowledge from the various specialties. The investigators will study the therapy of autoimmune disease by blocking co-stimulatory signals with CTLA4Ig and by blocking T cell activation with rapamycin. This strategy has two advantages. First, these are antigen non-specific steps in T cell activation and immune responses. This means that tolerance can be achieved without needing to know the identity of the antigen. Second, restricted delivery of signal two and alteration in cytokine production and profiles are probably involved in normal mechanisms of self tolerance. Third, by inhibiting T cell activation with rapamycin, in addition to co-stimulatory signal blockade, they may be able to induce long-term tolerance by allowing the occurrence of activation-induced cell death. The human diseases that our program will focus on are multiple sclerosis (MS), autoimmune diabetes (IDDM), and psoriasis. All are organ-specific diseases where T cells appear to be essential in initiating the immune response and lead to the particular disease pathology. *Project 1* is the clinical trials project, in which we propose a clinical trial of CTLA4Ig in diabetes, a clinical trial of CTLA4Ig + rapamycin in early MS, and describe the available patients and facilities for a potential psoriasis trial. The goals of *Project 2* are to investigate the role of NK T cells in human diabetes. *Project 3* will take a direct approach by cloning T cells and NK T cells from the pancreas and pancreatic lymph nodes of patients with diabetes. The approach of treating autoimmune diseases by preventing T cell activation is timely and has a high likelihood of success. There is a body of evidence, including clinical trials, supporting the use of CTLA4Ig in autoimmune disease, and also evidence for the synergistic role of rapamycin. The data obtained from the clinical trials and the critical information from the basic science projects will be valuable in getting us closer to our goal of tolerance induction for autoimmune disease.

▶ Title: *Suppression and Exacerbation of B- and T-Cell Responses* NIAID
P.I.: Ignacio Sanz, M.D.
Institution: University of Rochester, New York
Grant No.: 5 U19 AI056390-02
Study Type: Clinical
Award: $60,000

The overarching goal of this proposal is to establish an Autoimmunity Center of Excellence at the University of Rochester. This goal is based upon our belief that the understanding of human autoimmunity requires the concerted effort of basic and clinical scientists working together in an intellectual framework that provides constant feedback between bench studies and therapeutic interventions. Our center will concentrate on studies relevant to the pathogenesis and treatment of type 1 diabetes mellitus (T1DM), multiple sclerosis (MS), and systemic lupus erythematosus (SLE). Both types of studies are based on the unifying idea that abnormalities of B- and T-cell function are at the core of these autoimmune diseases. *Basic Project 1* will investigate the role of regulatory T cells (Treg) in the pathogenesis of T1DM and will generate new re-agents that will allow investigators to more specifically identify human Treg cells. *Basic Project 2* will elucidate the role of IL-12p40 monokines in MS and determine whether defects in Treg function exist in patients with this disease. *Basic Project 3* will study B-cell homeostasis and the cellular origin of disease-specific autoantibodies in SLE. In addition, this project will investigate whether abnormal Treg function contributes to the activation of autoimmune B cells and T cells in SLE. These pathogenic mechanisms will serve as the theoretical basis for our clinical trials. *Clinical Project 1* will study the clinical and immunological consequences of B cell depletion in SLE using the anti-CD20 monoclonal antibody Rituximab. *Clinical Project 2* will test the clinical and immunological effects of anti-IL-12 in patients with MS. We expect that the studies proposed will result in information that will not only improve our understanding of the disease in question but will also suggest new avenues of research for the other autoimmune diseases targeted by our center.

▶ Title: *Modulation of B-cell Responses in Autoimmunity* NIAID
P.I.: Eugene W. St. Clair, M.D.
Institution: Duke University, Durham, NC
Grant No.: 5 U19 AI056363-02
Study Type: Clinical
Award: $60,000

The proposed center will focus on the modulation of B-cell responses in autoimmunity. In autoimmunity, B cells not only serve as the source of pathogenic autoantibodies, but they also may function as antigen-presenting cells (APCs) and stimulate pathologic inflammation through a variety of mechanisms. B-cell function is regulated via the B-cell receptor complex, as well as other B-cell-specific cell surface ZAI1 CL-I (M2) 3 1 U19 AI056363-01 ST CLAIR, E antigens, including CD20 and CD22. Growing evidence, including our results, indicates CD20 and CD22 are attractive targets for immunotherapy of autoimmune diseases. In addition, the investigators have shown inflammatory stimuli, such as tumor necrosis factor α (TNFα), can promote the emigration of B cells from the bone marrow, transferring large numbers of developing B lymphocytes to the periphery. We hypothesize aberrantly activated B cells are pivotal to the clinical expression of autoimmunity, and the resulting inflammatory state affords an environment for abnormal development of autoreactive B cells and further dysregulation of the immunological response. Two interrelated basic research projects are proposed to investigate this hypothesis. Dr. Thomas Tedder, Professor and Chair of Immunology, will direct a project examining the roles of CD20 and CD22 in the regulation of B-cell function in mouse, taking advantage of a unique panel of CD20 and CD22-directed monoclonal antibodies developed in his laboratory. The other project will be headed by Dr. Garnett Kelsoe, Professor of Immunology, and will investigate to what extent inflammatory stimuli, such as TNFα, influence the trafficking of immature B cells and selection of the autoreactive B-cell repertoire. A clinical component led by Dr. St. Clair and other experienced physician-scientists will complement the basic research projects. This group has expertise in rheumatoid arthritis (RA), systemic lupus erythematosus, pemphigus vulgaris (PV), and other autoimmune diseases, as well as access to many different patient populations for clinical studies. One of the proposed trials will evaluate the safety and clinical efficacy of anti-CD22 monoclonal antibody therapy for RA, while the other will investigate infliximab (anti-TNFα) therapy for PV. Each of the trials includes mechanistic studies that are integrated with the goals of the basic research projects, providing synergy within the center. An administrative core will oversee the management of these projects. Overall, the proposed center will efficiently bridge basic and clinical investigations and should produce new insights into the immunotherapy of autoimmune disease.

▶ Title: *University of Alabama at Birmingham Autoimmunity Center for Excellence* NIAID
P.I.: Robert H. Carter, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 5 U19 AI056542-02
Study Type: Clinical
Award: $60,000

The University of Alabama at Birmingham (UAB) has an outstanding record in basic immunology and in testing of novel, translational therapies for autoimmune diseases. The UAB Autoimmunity Center of Excellence (ACE) is a multidisciplinary, collaborative program to unite these strengths to accelerate the development and testing of translational therapies for autoimmune disease. To accomplish this, the UAB ACE will promote basic and translational research and sponsor clinical trials of novel immunomodulatory agents. As part of this mission, the UAB

ACE will foster communication between basic and clinical investigators and between those focused on different immune-mediated diseases at UAB and nationally. Four projects are proposed. The Clinical Component (Project 1) includes highly experienced investigators from six clinical areas. Two potential clinical trials are proposed, targeting Death Receptor 5 in lupus, an approach developed at UAB; and IL-1 in psoriatic arthritis, using a high affinity blocker brought to UAB investigators by the pharmaceutical industry. Three basic projects center on the unifying theme of analysis of the interaction of T cells and cytokines and/or TNF-family factors in maintenance or restoration of tolerance, including: Project 2) function of Death Receptor 5 on activated T cells in autoimmunity; Project 3) the role of cytokines and TNF-family proteins in reconstitution of T cell tolerance after immunosuppression; and Project 4) the function of IL10-expressing T cells in tolerance in mucosal immunity. The interactive nature of these projects is illustrated by the fact that each basic project involves assays or models derived from at least one of the others. The Administrative Core will coordinate ACE activities, facilitate interactions and collaborations, promote scientific development, set the strategic agenda, and perform continuous evaluation of ongoing projects. The Immunomodulatory Studies Core will promote analysis of changes in cells or cytokines in human tissues in disease and in mechanistic studies of participants receiving biologic therapies. Both cores will serve all proposed projects. Thus, the ACE will unite UAB investigators to bring the strength of immunological research and the breath of experience in clinical trials in a range of immune-mediated diseases to jointly develop new therapies for autoimmunity.

▶ Title: *An Animal Model for Graves' Disease/Ophthalmology* NEI
P.I.: Juan C. Jaume, M.D.
Institution: UCSF/VAMC, Department of Medicine, San Francisco, CA
Grant No.: 5 R03 EY014962-02
Study Type: Basic
Award: $126,000

The ophthalmopathy of Graves' disease is a disfiguring, sight-threatening condition of unclear pathogenesis and not specific or definitive therapy. Graves' disease primarily manifests with hyperthyroidism that results from the stimulation of the TSHR by specific autoantibodies that mimic the effect of TSH. Often the ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves' disease exists. Recently, an animal model has been developed in which a proportion of individuals manifest immunological and endocrinological features of Graves' disease. We have generated and extended such mouse model. The overall goal of this proposal is to use this Graves'-like animal model to investigate critical issues of Graves' disease as is Graves' ophthalmopathy as follows: 1) Graves' ophthalmopathy in the Graves'-like mouse model. New observations suggest the immunizing cells used in the model behave as APC that constitutively express B7-1 molecules and bias the immune response to a Th1 type. These APC also have the capacity of presenting non-specific antigens present in culture medium. With this information we have modified our immunization protocol to improve specific (TSHR) antigen presentation and deviate the immune response to a Th2 type characteristic of human Graves'. We propose to: a) study the development of Graves' disease/ophthalmopathy in both, Th1 and Th2 settings, b) examine the role of CD40 for orbital fibroblast-B/T cell cross talk, and c) study the regulation of TSHR in orbital fibroblasts/preadipocytes. 2) Characterize TSHR antibodies in their relationship to Graves' ophthalmopathy.

Infectious Diseases

▶ Title: *A Prospective Study of Chronic Fatigue Syndrome in Adolescents* NIAID
P.I.: Renee R. Taylor, Ph.D., M.A.
Institution: University of Illinois at Chicago
Grant No.: 1 R01 HD043301-01A1
Study Type: Clinical
Amount: $300,000

This project will prospectively study the relationship between infection with mononucleosis and the onset and course of chronic fatigue syndrome (CFS) over time in adolescents. The following hypotheses will be tested using a prospective, case-control design: 1) Baseline predictors of post-infectious CFS and fatigue severity at 6 months will include greater levels of baseline psychological distress, having a psychiatric diagnosis at baseline, a greater degree of stressful life events at baseline, and higher levels of activity prior to initial infection; 2) Adolescents with CFS, compared with matched controls, will report higher levels of psychological distress, higher rates of psychiatric diagnoses, a greater degree of stressful life events, and lower levels of physical activity following infection at the 6-,12-, and 24-month time points; and 3) Compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol (peak and trough), reduced natural killer cell function and count, and elevated proinflammatory cytokines at the 6-, 12-, and 24-month time points. At the 6-month time point (clinic visit), adolescents with CFS will also demonstrate higher rates of orthostatic intolerance; and 4) In response to an exercise challenge test at the 6-month time point, compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol and plasma ACTH, and elevated cytokines—illustrating impaired communication between neuroendocrine and immune systems with physical stress. An exploration of the nature and timing of these relationships would provide a preliminary model of etiology and natural course of illness for adolescents with post-viral CFS. Results from this investigation may assist physicians in identifying adolescents at high risk for CFS and allow them to initiate preventative measures.

▶ Title: *Sex in Viral Myocarditis* NIAID
P.I.: Sally A. Huber, Ph.D.
Institution: University of Vermont, Burlington
Grant No.: 5 R21 AI51850-03
Study Type: Translational
Award: $50,000

Myocarditis is an inflammatory disease of the myocardium. Approximately 65 percent of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes, while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN) gamma and female cells producing interleukin-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

▶ Title: *Seroprevalience/Incidence of Genital Herpes* FIC
P.I.: Edith Nakku-Joloba
Institution: New Mulago Hospital, Uganda, Africa
Grant No.: 5 R01 TW006672-02
Study Type: Public health, clinical
Award: $20,000

Prevalence of herpes simplex type 1 and 2 virus (HSV-1 and -2) infection is high worldwide and is highest in developing countries like Uganda. International and local health organizations have called for studies to characterize genital herpes epidemiology in sub-Saharan Africa. Population estimates are needed for policy, for planning interventions, for valid measures of the effect of interventions, and for research on new therapies and potential vaccines. The overall goal of this study is to determine the burden of infection and assess the modifiable risk factors associated with Herpes simplex types 1 and 2 infection in Kampala, Uganda, with an aim of prevention of spread and relief of those who suffer with genital herpes. The proposed study will aim to: 1) estimate the age- and sex-specific prevalence of HSV-1 and -2; 2) estimate the incidence of HSV-1 and -2 in an inception cohort of HSV-2-negative persons in an urban population in Uganda; and 3) identify modifiable risk factors associated with HSV-1 and -2 prevalence and incidence in this population. The proposed study will be a two-stage stratified random population sample survey of female and male participants, 15 to 65 years old, in Kawempe division of Kampala District. To estimate prevalence of HSV-1 and -2, a cross-sectional serological survey at baseline will be done using type-specific ELISA tests for HSV-1 and -2. Incidence will be assessed in an inception cohort of HSV-2-negative persons by six monthly testing for HSV-2. Risk factors for genital herpes will be assessed using a standardized questionnaire to collect information on age; sociodemographic characteristics; sexual behavior; sexual partner characteristics, such as age differentials; and HIV-infection status. Incidence densities and relative risks will be calculated from new HSV-2 infection and risk factors that predispose to HSV-2 incidence, such as age, sex (gender), sexual behavior, and HIV infection analyzed in a Cox proportional hazards model. By conducting a population study in an urban area in a country where rural studies show high prevalence, we will describe the epidemiology genital herpes, gaining new knowledge about genital herpes in urban Uganda, and highlighting the modifiable risk factors which can be targeted for effective interventions.

Menopause

▶ Title: *Effects of Botanicals on Cognition in Midlife Women* NCCAM
P.I.: Pauline Maki, Ph.D.
Institution: University of Illinois at Chicago
Grant No.: 1 R21 AT001868-01A1
Study Type: Basic, clinical
Award: $194,837

The broad, long-term objective of this program of research is to better understand the effects of hormone therapy (HT) and alternative botanical supplements on cognition and brain functioning in early postmenopausal women. The specific aims of this research project are to quantify and compare the effects of the botanical menopausal treatments, black cohosh and red clover, and standard HT, Prempro® (conjugated equine estrogen plus medroxyprogesterone acetate), on neuropsychological and neuroimaging outcomes. The proposed design is a randomized, double-blind, placebo-controlled clinical trial. The cognitive study is conducted as an ancillary study to the NIH-funded study, A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to

Determine the Efficacy of Black Cohosh, Red Clover, and Prempro in the Management of Hot Flashes. Participants will include up to 28 women in each study arm—placebo, Prempro®, black cohosh, and red clover—for a total of up to 112. The primary outcome measures will be scores on standardized neuropsychological tests and patterns of brain activation during performance of verbal memory tests. Before treatment and at the end of the 12-month treatment period, participants will complete a 1.5-hour battery of neuropsychological tests that have been shown in previous studies to be sensitive to the effects of HT and menopausal symptoms. Half of the participants (n = 60) will also complete neuroimaging assessments using functional magnetic resonance imaging (fMRl) before and after the 12-month treatment period. The tasks performed in the MRI scanner will be verbal and figural memory tasks shown to be sensitive to HT in midlife women. Findings of group differences in the patterns of brain activation (i.e., regional blood flow changes) will point to the brain areas subserving any treatment-related improvements in memory performance. Recent findings of significant health risks associated with Prempro® heighten the need for research into the effects of alternative therapies for menopausal symptoms on cognitive outcomes.

▶ Title: *The Study of Women's Health Across the Nation (SWAN III)* NIA
P.I.: Kim Sutton-Tyrrell
Institution: University of Pittsburgh, PA
Grant No.: U01 AG012553
Study Type: Clinical
Award: $250,000

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic, community-based longitudinal study designed to characterize the biological, symptomatic, and psychosocial changes that occur during the menopausal transition and the effects of these changes on women's health during and after the transition. Current and prior funding (SWAN I and II) has supported a baseline and six annual follow-up examinations during which 895 (48 percent) women will have transitioned to postmenopause. This application requests funding to complete four additional follow-up visits (SWAN III) to allow an adequate evaluation of the late perimenopause and early postmenopause, a period that has not been well studied, particularly among non-white women. We will continue our current tracking of changes in reproductive hormones, bleeding patterns, symptoms, bone loss, cardiovascular (CV) risk factors, blood pressure, body size, and other related characteristics, and will undertake new scientific endeavors in targeted areas. These include measurement of vascular stiffness to assess early CV disease, assessment of vertebral morphometry at four sites using DEXA technology, and the addition of one cognitive function test. In addition, we will focus on linking the midlife experience to age-related outcomes (e.g., cognitive function, urinary incontinence) and chronic diseases (e.g., fractures, diabetes, and hypertension). Specimens from the additional follow-up visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples, as well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (2 years following the final menstrual period), we will shift from an annual to a bi-annual follow-up examination schedule with mail and telephone contact in the alternating years. This will permit cost-effective and less intensive followup. SWAN's organization and operations have been modified to enhance productivity and we are poised to publish important biological, symptom, and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. We will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN III.

▶ Title: *Phytoestrogens and Progression of Atherosclerosis* NCCAM
P.I.: Howard N. Hodis, M.D.
Institution: University of Southern California, Department of Medicine, Los Angeles
Grant No.: 5 U01 AT001653-02
Study Type: Clinical
Award: $200,000

The fear and discontent with traditional hormone replacement therapy (HRT), coupled with the interest in natural products, has resulted in an increased use of soy protein as a postmenopausal therapeutic alternative by both women and their physicians alike. Evidence from epidemiological and non-humane primate studies indicate that isoflavone-rich soy protein has antiatherogenic activity, evidence supported by a large body of data that indicate mechanistic and biologic plausibility. No studies to knowledge have been published or proposed to determine the long-term effects of soy protein on the progression of atherosclerosis in postmenopausal women. The investigators propose to conduct a 2.5 year, randomized, double-blind, placebo-controlled trial of isoflavone-rich soy protein in 300 healthy postmenopausal women without clinical evidence of cardiovascular disease. They hypothesize that relative to placebo, isoflavone-rich soy protein (supplying genistein, daidzein, and glycitein) will reduce the progression of subclinical atherosclerosis in healthy postmenopausal women. The primary end point will be the progression of subclinical atherosclerosis measured as the rate of change in common carotid artery intima-media thickness in computer image processed B-mode ultrasonograms, a well-established noninvasive arterial imaging end point for antiatherosclerosis trials, Isoflavone-rich soy protein may provide a safe and effective alternative approach for extending premenopausal ardioprotection afforded by endogenous estrogen into menopause without the increased risk of thromboembolic events and certain cancers associated with traditional HRT. Since many postmenopausal women are using spy products to maintain their health, it is important to understand whether soy protein has an antiatherogenic effect so that women can make a truly informed decision concerning their expectations of this form of postmenopausal therapy. The question as to whether soy protein is effective in reducing progression of atherosclerosis in postmenopausal women is not only timely, but also of immense medical and financial importance since atherosclerosis remains the number one killer of postmenopausal women.

Mental Health

▶ Title: *Evidence-based Practice Report on Eating Disorders* AHRQ
P.I.: Kathryn Lohr, Ph.D.
Institution: Research Triangle Institute, University of North Carolina, Durham
Study Type: Policy Analysis
Award: $250,000

Eating disorders primarily affect young girls and women, but can affect males as well. Sex and gender-based differences will be evaluated in this report. In terms of major areas of focus, three types of eating disorders will be evaluated: bulimia nervosa, anorexia nervosa, and binge eating. Evidence will be reviewed relating to whether one type of treatment or combination of treatment modalities is more effective for these disorders. Identification of predictors of increased relapse risk or hospital re-admission will be assessed, and what variables improve both short- and long-term patient outcomes.

▶ Title: *Estrogen Influences on Neural Precursor Cell Development* NIMH
P.I.: C. Dominique Toran-Allerand, M.D., Sc.D.
Institution: Columbia University, College of Physicians and Surgeons, New York, NY
Grant No.: 1 R21 MH071381-01
Study Type: Basic
Award: $222,179

The proposed studies are designed to obtain preliminary data concerning the actions of estrogen on the development of progenitor cells of the adult rat hippocampal dentate gyrus. 17β-estradiol reportedly enhances granule cell neurogenesis (the formation of new neurons) in the adult female rat hippocampal dentate gyrus. The cellular mechanisms and estrogen receptor(s) mediating this hormonal action are not known. The investigators have shown that 17β-estradiol and its transcriptionally inactive, natural stereoisomer 17α-estradiol elicit rapid and transient activation of the mitogen-activated protein kinase and phosphatidylinositol 3″-kinase-Akt signaling pathways in postnatal rodent neocortical cultures and neural progenitor cells of the adult rat hippocampal dentate gyrus. These responses appear to be mediated by a putative estrogen receptor (ER), "ER-X", which is distinct from the intranuclear estrogen receptors ER-α and ER-β. "ER-X" is plasma membrane associated and developmentally regulated and returns following ischemic brain injury. Progenitor cells of the adult rat hippocampal gyrus are enriched in "ER-X" protein and lack ER-α and ER-fl mRNA and protein. The investigators propose a series of integrated and complimentary cell biological and biochemical analyses to compare the actions of 17α- and 17β-estradiol on the development of progenitor cells. They hypothesize that "ER-X" and 17α-estradiol, its preferred ligand, play an important role in the development and remodeling of the hippocampus. This hypothesis will be tested by focusing on the effectiveness of 17α-estradiol in comparison with 17β-estradiol with respect to i) neurogenesis, ii) neuronal differentiation, and iii) the intracellular signaling pathways that mediate these actions. The expression of "ER-X" in the adult hippocampal dentate gyrus suggests that its developmental role could be reactivated to enhance functional hippocampal remodeling in the course of disorders of cognition, mood, and affect, such as major depression and bipolar disorder, conditions that may be associated with estrogen, since they are more frequent in females. Unlike 17β-estradiol, 17α-estradiol has little affinity for ER-α or ER-β and may be more effective and therapeutically safer. The results of these experiments will enable drug development and treatment of children and adults of both sexes without fear of undesirable effects mediated by ER-α or ER-β.

▶ Title: *Brain LC-PUFAs and Maternal Mental Health* NIMH
P.I.: Beth Levant, Ph.D.
Institution: University of Kansas Medical Center
Grant No.: 1 R01 MH71599-01
Study Type: Basic
Award: $243,827

Alterations in brain long chain polyunsaturated fatty acid (LC-PUFA) composition, particularly decreased docosahexaenoic acid (DHA), are implicated as a contributing factor in depression and psychosis. Preliminary data indicates that pregnancy and lactation can deplete the maternal brain of DHA. Accordingly, these studies are designed to test the hypothesis that depletion of maternal brain DHA during pregnancy and lactation contributes to postpartum mental illness. The Specific Aims will use a rat model to: 1) Determine the effects of pregnancy and lactation

on levels of maternal brain DHA and other LC-PUFA. Manipulation of dietary fatty acid content will be used to alter maternal brain DHA levels. LC-PUFA will be assessed in four brain regions associated with depression and psychosis, as well as in erythrocytes. These studies will establish a rodent model with which to study the effects of depleted brain DHA levels following pregnancy and lactation on neurochemical parameters associated with depression and psychosis in humans. 2) Determine the effects of reduced brain DHA in the postpartum period on maternal hypothalamic-pituitary-adrenal (HPA) axis activity and regulation. Regulation of the HPA axis will be assessed using a modification of the dexamethasone suppression test. The affinity and density of cerebral cortical corticotrophin releasing factor1 (CRF1) receptors will also be quantified. 3) Determine the effects of reduced brain DHA in the postpartum period on monoamine neurochemistry. The concentrations of serotonin, norepinephrine, and dopamine (and their respective metabolites) will be measured in brain regions relevant to depression or psychosis. The affinity and density of receptors most strongly implicated in depression or psychosis (5-HT1A, 5-TH2A, p, D2, and D_) will also be quantified. 4) Determine the effects of reduced brain DHA in the postpartum period on expression of brain-derived neurotrophic factor (BDNF) in hippocampus. Hippocampal expression of the BDNF gene, which is decreased in animal models of depression, will be measured by RNAse protection assay. These experiments will determine whether reproductive activity and the resulting alterations in maternal brain LC-PUFA content are likely to contribute to postpartum mental illness in women. Findings will point to causes of postpartum mental illness and thus the identification of women at risk and the elimination of risk factors. These findings will also suggest novel treatments for such illnesses when they occur.

▶ Title: *Health Survey of Two-Spirited Native Americans* NIMH
P.I.: Karina L. Walters, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 5 R01 MH65871-03
Study Type: Clinical
Award: $175,000

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the United States. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to: 1) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); 2) test the direct associations between trauma and health outcomes; 3) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and 4) examine the mediating role of substance use on the trauma–HIV sexual risk behavior and trauma–mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

Musculoskeletal Systems

▶ Title: *Regulation of PTH Activity in Bone by B-arrestin* NIAMS
P.I.: Mary L. Bouxsein, Ph.D.
Institution: Beth Israel Deaconess Medical Center, Boston, MA
Grant No.: 1 R01 AR049265-01A1
Study Type: Basic
Award: $99,999

Parathyroid hormone (PTH) is a major regulator of mineral homeostasis and bone metabolism. Intermittent PTH therapy is approved for treatment of osteoporosis, yet the cellular mechanisms underlying the biologic effects of PTH are not completely understood, including the molecular basis for the observation that low-dose, intermittent administration of PTH elicits net bone formation, whereas continuous administration of high-dose PTH causes predominantly bone loss. The biological actions of PTH are mediated by a G protein-coupled receptor (PTH1R). The investigators demonstrated that a cytoplasmic molecule, β-arrestin2 (β-arr2), regulates the activity of PTH1R and its agonists *in vitro* by promoting rapid endocytosis of ligand-receptor complexes and by inhibiting CAMP signaling in response to agonists. In this revised application, the investigators present preliminary data showing that compared to wild-type mice, β-arr2 null mice have reduced bone mass and an altered bone response following intermittent PTH administration. In addition, osteoblasts from mice null for β-arr2 exhibit increased and sustained CAMP signaling in response to PTH. The investigators, therefore, hypothesize that β-arrestin2 is a key modulator of the biologic activity of PTH in bone. The investigators will pursue three specific aims to test this hypothesis: 1) Determine the role of β-arr2 in regulating the anabolic response of bone to intermittent PTH, by determining the response of ovariectomized β-arr2 KO and WT mice to intermittent PTH therapy. 2) Determine the cellular and molecular mechanisms of PTH biologic activity in primary osteoblastic cell cultures from β-arrestin2 KO mice. 3) Determine the effects of targeted overexpression of β-arrestin2 in osteoblasts on the skeletal response to intermittent and continuous PTH administration in ovariectomized and intact mice, respectively. In summary, the overall goal of this project is to improve our understanding of the mechanisms regulating the biologic activity of PTH in bone. By conducting complementary *in vivo*, *ex vivo*, and *in vitro* experiments in mice deficient for β-arrestin2 and in mice overexpressing β-arrestin2, specifically in bone, the investigators will provide novel insights into potential mechanisms that underlie the distinct skeletal response to intermittent versus continuous PTH administration. Information gained from the proposed studies will be instrumental for the development of new PTH1R ligands with improved signaling and biologic activity profiles for treatment of osteoporosis and other metabolic bone disorders.

▶ Title: *Osteoarthritis Initiative* NIAMS
P.I.: Michael Nevett, Ph.D., Coordinating Center (University of California, SF) (University of Maryland School of Medicine, Baltimore; March Hochberg, M.D., Ohio State University, Columbus; Rebecca Jackson, M.D., University of Pittsburgh; C. Kent Kwoh, M.D. and Memorial Hospital of Rhode Island, Pawtucket; Annlouise Assaf, Ph.D., F.A.H.A.)
Study Type: Clinical
Award: $800,000

The Osteoarthritis Initiative (OAI) is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis (OA), a degenerative joint disease that is a major cause of disability in people 65 and older.

Over 5 to 7 years, the OAI will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

▶ Title: *Low-dose Doxycycline Effects on Osteopenic Bone Loss* NIDCR
P.I.: Jeffrey B. Payne, D.D.S.
Institution: University of Nebraska, Lincoln
Grant No.: 5 R01 DE12872-04
Study Type: Translational, clinical
Award: $384,609

Osteoporosis represents a major public health problem in the United States. Osteoporosis is associated with decreased systemic bone mineral density (BMD), an increased incidence of vertebrae, wrist and hip fractures, and tooth loss. The dominant pathogenic factor for osteoporosis in postmenopausal women is estrogen (E2) deficiency. In longitudinal NIH-supported clinical trials, we have shown accelerated alveolar crestal bone height and density loss in postmenopausal, E2- deficient women with a periodontitis history relative to E2-sufficient women, and in osteoporotic/osteopenic women versus women with normal lumbar spine BMD. Because of this relationship between E2-deficiency, osteoporosis, and oral bone loss, it is desirable to test therapeutic strategies to mitigate alveolar bone loss in postmenopausal women. A recent discovery by Dr. Golub (Co-PI) showed that tetracyclines, including low-dose doxycycline (LDD), by virtue of a non- antimicrobial property, can: 1) inhibit host-derived, tissue-destructive matrix metalloproteinases (MMPs), including collagenases, involved in bone resorption; and 2) stimulate osteoblast activity and bone formation. These biological properties make tetracyclines compelling candidates for use in postmenopausal women with periodontitis. Therefore, the objective of this research is to investigate the therapeutic potential of LDD in postmenopausal osteopenia and periodontitis, diseases characterized by excess collagen breakdown and bone resorption. The hypothesis of this proposal is that LDD (compared to placebo) can improve radiographic, clinical, and biochemical parameters of periodontitis in E2-deficient, osteopenic postmenopausal women with periodontitis. Accordingly, the specific aim of this proposal is to use a 2-year double-blind, placebo-controlled trial of E2-deficient women to determine the effect of LDD on: 1) alveolar bone crestal and subcrestal density (measured by computer-assisted densitometric image analysis), and linear alveolar crestal bone height; 2) clinical periodontal measurements such as probing depth and relative clinical attachment level; and 3) gingival crevicular fluid markers of bone turnover (e.g., C-terminal telopeptide pyridinoline crosslinks [ICTP, a collagen breakdown fragment]). As a secondary aim, the study will evaluate the effect of LDD on systemic bone mineral density at the lumbar spine and femoral neck by dual-energy x-ray absorptiometry (DEXA) and the effect of LDD on serum and urine biochemical markers of bone turnover.

▶ Title: *Bone-sparing by Ca Salts with and without Extra Phosphorus* NIAMS
P.I.: Robert P. Heaney, Ph.D.
Institution: Creighton University Department of Medicine, Osteoporosis, Omaha, NE
Grant No.: 5 R01 AR048846-02
Study Type: Clinical
Award: $75,000

Bone mineral is basically calcium phosphate; and both Ca and P are required for bone acquisition. Typical Ca intakes in the United States are lower than current recommendations, and typical P intakes, higher. To test the possible importance and value of supplementing both of the components of bone mineral in support of anabolic therapy of osteoporosis, we propose a 1-year randomized trial, comparing, in two groups of teriparatide-treated postmenopausal osteoporotic women, calcium supplements with and without extra phosphorus (i.e., Ca phosphate vs. Ca carbonate). The principal outcome measure will be change in bone mineral content over the 1 year of the trial. A secondary outcome is measurement of bone resorption biomarkers so as to assess whether the phosphate salt elevates remodeling relative to the carbonate salt. A finding of superiority of the phosphate-containing Ca supplement would provide evidence leading to a cost-neutral change in Ca sources and a corresponding improvement in osteoporosis co-therapy (and possibly osteoporosis prophylaxis, as well).

▶ Title: *Bone-sparing Effects of Soy Phytoestrogens in Menopause* NIAMS
P.I.: Silvina Levis, M.D.
Institution: University of Miami School of Medicine, Department of Medicine, FL
Grant No.: 5 R01 AR048932-02
Study Type: Clinical
Award: $100,000

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years is well established. Although hormone replacement therapy (HRT) can spare women some of these complications, the Women's Health Initiative findings indicate significant potential health risks, risks that prompt more and more women to turn from prescribed HRT to over-the-counter products in the hope that soy phytoestrogens and other "estrogens" from natural sources can replace prescription estrogens in terms of benefits while sparing critical side effects. In spite of the fairly widespread and now rapidly growing use of phytoestrogens, major gaps remain in our knowledge of their long-term efficacy and safety. It is proposed to conduct a "Soy Phytoestrogens As Replacement Estrogen (SPARE)" study in young menopausal women to evaluate the effectiveness of a 2-year treatment with purified soy isoflavones in preventing bone loss. The study will also explore the effectiveness of oral isoflavones in preventing menopausal symptoms and other changes associated with estrogen deficiency. The study will characterize the actions of a defined preparation of soy isoflavones in humans and will correlate these actions with the circulating serum levels of the principal isoflavone metabolites, providing new insights on their long term biological actions. This 5-year study will provide a foundation of knowledge from which menopausal women can begin to make more informed decisions regarding HRT and menopausal signs and symptoms.

Obesity/Overweight

▶ Title: *Longitudinal Assessment of Bariatric Surgery (Expansive)* NIDDK
P.I.: Steven H. Belle, M.D.
Institution: University of Pittsburgh, PA
Grant No.: 5 U01 DK066557-02
Study Type: Clinical
Award: $300,000

The Bariatric Surgery Clinical Research Consortium (BSCRC) is being established to "facilitate coordinated clinical, epidemiological, and behavioral research in the field of bariatric surgery". The consortium will include four to six collaborating clinical centers, a NIDDK Project Scientist, and a Data Coordinating Center (DCC). This consortium will work cooperatively to create a core information base, collected under a common protocol, on patients undergoing bariatric surgery and a non-surgical control group. The consortium members will also participate in one to two clinical research projects each year. The DCC will work with the BSCRC members to support all aspects of study design, study conduct, and data analysis for the central information core and each clinical research project. The DCC will develop a distributed data entry system and will maintain a secure, central database of clinical, laboratory, and surgical information, and serum and tissue sample inventories. The DCC will identify and contract with central laboratory(ies) and either coordinate with the Central NIDDK Biosample Repository or identify and contract with another repository. The DCC will develop safety and efficacy analysis plans and will prepare materials for presentations at BSCRC-related meetings, scientific conferences, and for publications and regulatory bodies. The DCC will coordinate all activities of the consortium, including meetings and conference calls for the executive committee, steering committee, subcommittees, and presentations to the data and safety monitoring board. Finally, they will share data collected for the BSCRC with the wider scientific community and archive all data, study intervention materials, and coordinate archiving all specimens at the end of the study.

▶ Title: *Look AHEAD (Action For Health in Diabetes)* NIDDK
Institution: Wake Forest University (coordinating center), Winston Salem, NC
Johns Hopkins University, Baylor College of Medicine, University of Colorado Health, University of Washington, University of Tennessee, St. Lukes-Roosevelt Institute, University of Alabama at Birmingham, The Miriam Hospital, Pennington Biomedical Research, University of Texas Health Science, University of Minnesota, University of Pittsburgh, Massachusetts General Hospital, University of California Los Angeles, University of Pennsylvania, and Southwest American Indian Center (12 clinical centers)
Grant No.: 5 U01 DK57136-06
Study Type: Clinical
Award: $100,000

Look AHEAD is a multicenter, randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education, and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke, and cardiovascular death.

Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life, and psychological outcomes. The cost and cost effectiveness of the Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

Opthalmic Diseases

▶ Title: *Incidence of Late Macular Degeneration in Older Women* NEI
P.I.: Anne L. Coleman, M.D.
Institution: University of California–Los Angeles
Grant No.: 5 U10 EY13626-03
Study Type: Epidemiologic (case-control)
Award: $230,000

Age-related macular degeneration (ARM) is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14-year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted, health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5,482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5 percent of these women have photographically validated late ARM, 41.5 percent have early ARM, and 54 percent have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEI-VFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30 percent of the eyes with ARM and 10 percent of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

▶ Title: *Estrogen Receptors and Maintenance of Lens Transparency* NEI
P.I.: Vicki L. Davis, Ph.D.
Institution: Cedars-Sinai Medical Center, Los Angeles, CA
Grant No.: 5 R01 EY014600-02
Study Type: Basic
Award: $131,297

Epidemiological studies suggest that estrogen may protect against age-related cataracts. The discovery of ocular estrogen receptors (ER) indicates that estrogen protection may result from direct interactions with its receptors in the eye. Studies in our transgenic mouse model validate the concept that estrogen is beneficial for the eye; these mice express a repressor (ERdelta3) that inhibits estrogen action, leading to cortical cataract formation. Although the ERalpha and ERbeta protein and/or RNA have been detected in ocular tissues, there has been no confirmation that these receptors are functional, since there are no known estrogen responsive markers in the eye. Therefore, in this proposal, we will use several transgenic mouse models to investigate the function of ERalpha and ERbeta in the lens. Our specific aims will examine two critical questions important for understanding the role of estrogen and its receptors in normal lens physiology and cataractogenesis: 1) Can estrogen induce an ER-mediated response directly in the lens? and 2) Are both ERalpha and ERbeta essential for maintenance of lens transparency? First, using ERIN transgenic mice, we will determine whether ERalpha, ERbeta, and ERdelta3 receptors can regulate expression of an estrogen-responsive reporter gene in the lens. The ERIN model expresses a beta-galactosidase reporter under the control of two consensus estrogen-response elements (ERE). The alphalERKO and betaERKO mice provide a means to segregate the individual ER subtypes to determine their individual roles in the lens. Therefore, the ERIN mice will be crossbred with alphaERKO, betaERKO, and ERdelta3 transgenic mice to document that each receptor influences estrogen-responsive gene expression in the lens. Next, we will investigate if both ERalpha and ERbeta influence spontaneous and ERdelta3-induced cataract development. We will examine aging alphaERKO, betaERKO, and alphabetaERKO mice to determine if loss of each or both receptors induces lens opacity. To ascertain if cataracts occur in our ERdelta3 mouse model due to inhibition of ERalpha and/or ERbeta activity, the ERKO lines will be crossbred with the ERdelta3 mice. These studies will verify that ERalpha, ERbeta, and ERdelta3 are expressed and functional in the lens. In addition, we will establish if both ERalpha and ERbeta have essential roles in preserving lens transparency. The concept that estrogen can provide protection against age-related cataracts is promising. This study will provide the gateway for future studies to investigate how exposure to various estrogens influence risk of age-related cataracts and the potential of estrogens as a therapy for cataract prevention.

Pain

▶ Title: *Mast Cell Role in Masseter Muscle Repair* NIDCR
P.I.: Joyce A. Morris-Wiman, Ph.D.
Institution: University of Florida, Gainesville
Grant No.: 1 R21 DE016317-01
Study Type: Basic
Award: $150,000

Temporomandibular disorders (TMD) affect approximately 12 percent of the U.S. population, predominately women in their childbearing years. Of those affected by TMD, greater than 60 percent have masticatory muscle pain as their main complaint. Mast cells have been demonstrated to be not only associated with a decrease in muscle viability after damage, but also may be responsible for pain associated with muscle inflammation. This proposal will examine events in masseter

and in limb muscle repair in response to a freeze injury, to detect differences that might explain the impaired repair capacity of the masseter and to examine how mast cell response may contribute to this decreased regenerative potential. Standardized injury models that duplicate naturally occurring muscle damage in masseter during bruxism are essential to our understanding of the processes that contribute to muscle inflammation and pain in TMD. We plan to test the hypothesis that the primary defect in masseter muscle repair resides in its inflammatory response to damage, manifested as increased numbers of mast cells and recurrent necrosis and resultant fibrotic repair. Further, we plan to examine events in masseter muscle repair in response to damage from concentric and eccentric contraction. This will allow us to experimentally test the hypothesis that concentric or eccentric contractions, such as those experienced during jaw clenching or bruxism, result in muscle fiber damage in the masseter that prompts a prolonged inflammatory response and delay in repair.

▶ Title: *Hormonal Cycles in Women: Effects on Temporomandibular Disorders Pain and Symptoms* NIDCR
P.I.: Linda Leresche, Sc.D.
Institution: University of Washington, Department of Oral Medicine, Seattle
Grant No.: 1 R01 DE016212-01
Study Type: Translational
Award: $130,000

This project will study the interactions of mind and body related to temporomandibular disorders (TMD), a group of painful conditions involving the muscles of mastication and the temporomandibular joint. These pain problems are about twice as common in women as in men in the community, and prevalence peaks during the reproductive years. The etiology of TMD pain is unknown, but psychological stress, depression, and the presence of other somatic complaints have been shown to influence the course of these disorders. Prior research suggests that female reproductive hormones may also influence TMD pain. Two related studies will investigate the cyclic nature of TMD pain in women. Study 1 will assess the relationship of pain to salivary levels of reproductive hormones and to psychological stress across two consecutive menstrual cycles for female TMD patients with normal menstrual cycles, as well as appropriate comparison groups of normally cycling women with episodic headache, and normally cycling control women without TMD, headache, or other chronic pain problems. Study 2 will manipulate the behavioral and hormonal factors that are hypothesized to influence TMD pain, comparing the effects of: 1) a continuous oral contraceptive intervention designed to suppress menses and stabilize the hormonal environment, 2) a self-management intervention focused on and timed to the chronobiology of TMD symptoms across the menstrual cycle, and 3) a usual self-management intervention not timed to biological events. The aims of this clinical trial are to shed light on the mechanisms underlying the cyclic nature of TMD pain and symptoms in women, as well as to determine which treatment modality results in the greatest improvement in TMD pain and symptoms.

▶ Title: *Twin Study of Chronic Widespread Pain* NIAMS
P.I.: Niloofar Afari, Ph.D.
Institution: Harbor View Medical Center, Seattle, WA
Grant No.: 1 R01 AR051524-01
Study Type: Clinical
Award: $99,999

Chronic widespread pain (CWP) occurs in 4 to13 percent of people and is one of the defining characteristics of fibromyalgia (FM). Although tender points were originally considered as essential to the diagnosis of FM, it is now felt that they reflect pain severity and distress, and that FM lies at one end of the CWP continuum. To truly understand the pathogenesis of CWP, it would

be optimal to study the entire spectrum of individuals who have this symptom. Another critical issue in the mechanistic study of CWP is what to study. Over the past two decades, FM researchers have described abnormalities in various components of the central nervous system, as well as high rates of psychological co-morbidities and other chronic multisymptom illnesses. The role and significance of each of these factors in predisposing to the illness, directly causing the symptoms or occurring as a consequence of the condition, are unclear. The complexity of FM and the continuum of CWP have led investigators to develop a theoretical model of CWP that is synergistic and multidimensional; predisposing factors are of particular interest in this model since these represent premorbid risk or protective factors that relate to the development of CWP. Further, predisposing factors can be differentiated from illness-associated features that occur as a consequence of the condition. A co-twin control study is a powerful means for examining specific hypotheses about the etiology and consequences of CWP derived from the theoretical model. Twenty-one MZ and 21 DZ twin pairs discordant for CWP, along with 22 MZ and DZ pain-free control twin pairs will be recruited from the population-based University of Washington Twin Registry. Twin pairs will undergo an intensive evaluation of the autonomic nervous system (ANS) function, hypothalamic-pituitary-adrenal (HPA) axis function, exercise capacity, sleep and activity levels, evoked pain processing, and psychiatric and psychosocial factors involved in CWP. There are two specific aims: 1) Assess similarities and differences in ANS function, HPA axis function, exercise capacity, sleep and activity levels, evoked pressure pain sensitivity, and psychiatric and psychosocial factors between female twins with CWP and their pain-free co-twins. 2) Determine if the association between CWP and the above illness characteristics is due to confounding by genetics or common environmental factors by comparing CWP-discordant MZ female twin pairs with CWP-discordant DZ and pain-free MZ and DZ pairs. Additionally, investigating the pattern of differences between twin groups can help to distinguish factors that are predisposing to CWP and those that occur after the onset of the illness.

▶ Title: *Pain Management in Temporomandibular Joint Disorders* NIDCR
P.I.: Jennifer Haythornthwaite, Ph.D.
Institution: Johns Hopkins University, Baltimore, MD
Grant No.: 5 R01 DE13906-04
Study Type: Clinical, behavioral
Award: $341,705

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

▶ Title: *Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)* NIDCR
P.I.: James R. Fricton, D.D.S., M.S.
Institution: University of Minnesota, Minneapolis
Grant No.: N01 DE22635
Study Type: Registry
Award: $100,000

The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR's TIRR) at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

▶ Title: *Sex Differences in Opioid Analgesia* NIDA
P.I.: Anne Z. Murphy, Ph.D.
Institution: University of Maryland School of Medicine, Baltimore
Grant No.: 5 R01 DA016272-03
Study Type: Basic
Award: $50,000

Chronic pain afflicts millions of people each year. Opioid-based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animal models of acute pain, the effective dose of morphine is approximately five to ten times greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in *Aim 1* will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in *Aim 2* will use neural tract tracing techniques to delineate the anatomical organization of the PAG-NRM spinal cord circuit in males and females. *Aim 3* will examine the functional organization of this circuit in a model of prolonged inflammatory pain. The PAG is enriched in opioid receptors. Studies proposed in Aim 4 will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. These studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex-based differences in opioid analgesia.

▶ Title: *Trigeminal Pain Mechanisms and Control* NIDCR
P.I.: Jon D. Levine, Ph.D.
Institution: University of California–San Francisco
Grant No.: 5 P01 DE08973-14
Study Type: Basic
Award: $163,734

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

Physical Activity

▶ Title: *Social Cognitive Theory and Physically Active after Endometrial Cancer Intervention* NCI
P.I.: Basen-Engquist, Karen M.
Institution: University of Texas MD Anderson Cancer Center, Houston
Grant No.: 1R01CA109919-01
Study Type: Clinical
Award: $100,000

Physical activity has been shown to benefit cancer survivors' physical and emotional well-being, however, few studies have focused on the process and determinants of the adoption of physically active (PA) lifestyles in cancer survivors populations. The goal of the project is to study predictors of adherence to physical activity in sedentary endometrial cancer survivors who receive an intervention to increase their physical activity. The specific aims of the study are: 1) to test a Social Cognitive Theory-based model of physical activity adoption among sedentary endometrial cancer survivors who receive an intervention to increase physical activity; 2) to elucidate the role of cardiorespiratory fitness and somatic sensations during physical activity on self-efficacy; 3) to determine whether intervention dose is related to physical activity adherence; and 4) to test the effects of adherence to physical activity on endometrial cancer survivors' quality of life. Two hundred sixty-seven sedentary Stage I-IIIa endometrial cancer survivors will be recruited to participate in this 6-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every 2 months to assess functional capacity and efficiency, physical activity, and Social Cognitive Theory-related variables. All participants will receive an intervention to increase their physical activity, consisting of a customized exercise prescription, telephone counseling, and written materials. Results of the study will provide a rigorous test of Social Cognitive Theory as it is applied to physical activity, and will inform the development of effective interventions for cancer survivors.

▶ Title: *Young Adult Environmental and Physical Activity Dynamics* NCI
P.I.: Popkin, Barry M.
Institution: University of North Carolina–Chapel Hill
Grant No.: 1R01CA109831-01
Study Type: Clinical
Award: $100,000

There is an increasing call for population-wide environmental/policy interventions to increase physical activity despite the lack of large-scale intervention or epidemiological research documenting the benefits of such changes. This longitudinal study will link contemporaneous geographic locations of respondents with physical environment variables and data from an exceptional dataset including quality physical activity data. Four study years (1985, 1992, 1995, and 2001) of the Coronary Artery Risk Development in Young Adults Study (CARDIA) will be used. This is a longitudinal study of the antecedents and risk factors for cardiovascular disease in an ethnicity-, age-, and sex-balanced cohort of 5,115 black and white young adults aged 18 to 30 years at baseline to examine relationships between environmental factors and physical activity. Complex longitudinal and spatial analytical models will be used to explore relationships between environmental factors and physical activity. A critical element addressed will be residential self-selection, an issue of increasing concern as scholars attempt to understand how the environment affects physical activity. The investigators will model physical activity as a function of covariates, some of which may be endogenous choices made by the individual. The investigators will examine race/ethnic differentials in these effects and the impact of "the environment" shifts over time and through the lifecycle. The focus will be on examining how modifiable environmental factors will affect physical activity patterns among underserved communities and, consequently, will reduce ethnic and socioeconomic differentials in health status. The longitudinal analysis and the vast array of environmental measures used, coupled with the very high quality physical activity measures of CARDIA, allow us to capture the effects of the environment (and changes in location) on physical activity shifts. No study heretofore has had large-scale groupings and in-depth environmental measures over time to examine these issues in a dynamic manner.

▶ Title: *Mediators and Moderators of Exercise Behavior Change* NCI
P.I.: Bryan, Angela
Institution: University of Colorado, Boulder
Grant No.: 1R01CA109858-01
Study Type: Clinical
Award: $100,000

Rates of cancer and cardiovascular disease have shown very little improvement over the past two decades, and the incidence of type 2 diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30 percent of total cancer deaths are related to poor exercise and nutrition, and other reports have suggested that, when taking into consideration both cardiovascular disease and cancer, inactivity contributes to as many as 250,000 premature deaths per year. Despite the benefit of regular physical activity in the prevention of cancer and other debilitating illnesses, 75 percent of the U.S. population do not get the recommended amount of physical activity (30 minutes of moderate intensity physical activity 5 or more days per week), and 40 percent of the population is completely sedentary. The objective of the proposed research is to understand the mediators and moderators of a well tested, individually tailored, print-based intervention to increase exercise behavior among sedentary adults. Using a randomized, controlled intervention trial, the proposed study will address three primary and one secondary hypotheses: 1) a previously tested and validated exercise promotion intervention is successful at helping sedentary individuals initiate and maintain a moderate intensity physical activity regimen, as compared to a health and wellness control intervention; 2) increases in positive attitudes, perceived normative support,

self-efficacy, and intentions to exercise will mediate the effectiveness of the intervention; 3) increased positive mood and better temperature, stress, and lactate regulation immediately after exercise challenge (assessed in the laboratory) will moderate the effectiveness of the intervention; and 4) secondarily, the investigators will test whether gender, race/ethnicity, and two recently suggested genetic factors (BDNF and OPRM1) moderate the effectiveness of the intervention. The rigorous assessment of how and for whom an exercise promotion intervention is effective will provide information for future development of intervention strategies and content, as well as allow the targeting of exercise content to individuals for whom it is most likely to be effective.

▶ Title: *Physical Activity Adherence in Black Women Over 65* NINR
P.I.: Karen J. Anderson, M.S.
Institution: University of Nebraska, Omaha
Grant No.: 1 F31 NR008969-01
Study Type: Clinical
Award: $34,228

The proposed dissertation study will be guided by Healthy People 2010 objectives in the physical activity focus area. The overall purpose of this study is to improve the health status of African American women, 65 to 85, through promoting adherence to healthy lifestyle behaviors, specifically physical activity. The specific aim of this study is to determine the impact of a physical activity intervention on self-efficacy for overcoming barriers and adherence to physical activity in this target population. A two-group, comparative experimental design with repeated measures at baseline, 6 months, and 1-year follow-up period on selected psychosocial and physiological outcomes per the conceptual model and hypotheses will be implemented. The candidate proposes to investigate the effects of a physical activity intervention on self efficacy to overcome barriers and promote adherence to physical activity among older African American women, a priority area for Healthy People 2010.

▶ Title: *Heart to Heart: An Exercise Intervention for Rural Women* NINR
P.I.: Cindy K. Perry, M.S.N.
Institution: Oregon Health Sciences University, Portland
Grant No.: 1 F31 NR008656-01A1
Study Type: Clinical
Award: $31,569

Women's participation in regular exercise is a major factor in preventing heart disease, the leading cause of death in women. Only 15 percent of adults exercise at the recommended level and the percentage for rural women is even less. Heart-to-heart (HTH) is an innovative intervention designed to increase exercise in rural women at risk of developing coronary heart disease. The specific aims of this research project are: 1) determine the magnitude of change in exercise adherence and cardiorespiratory fitness and whether this magnitude differs for rural women in HTH and rural women in the control group; 2) examine the magnitude of change in self-efficacy, stage of change, and social support and whether this change differs for rural women in HTH and rural women in the control group; 3) examine whether self-efficacy, stage of change, and social support mediate the relationship between HTH and the outcome variables of exercise adherence and cardiorespiratory fitness; and 4) describe HTH participants' experiences with the intervention. Data from exercise logs will measure adherence, a 12-minute walk test will measure fitness, and self-report data will measure self-efficacy, social support, and group cohesion. Quantitative data will be analyzed with ANOVA, hierarchical regression, and effect sizes. Qualitative data will be analyzed with qualitative content analysis.

▶ Title: *Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease* NHLBI
P.I.: Brian H. Annex
Institution: Medical Center, Durham, NC
Grant No.: 5 R01 HL075752-02
Study Type: Clinical
Award: $250,000

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5 percent of the U.S. population over 50. Approximately one-third of patients with PAD have typical claudication, defined as pain in one or both legs on walking that is relieved by rest. Patients with claudication have a marked impairment in exercise performance similar to patients with NYHA class III heart failure. Goals of treatment for PAD patients include risk-factor modification and antiplatelet drug therapy to address increased cardiovascular mortality risk. Supervised exercise training is the most efficacious treatment to improve walking capacity, demonstrated in many (small) randomized trials. Neither the pathophysiology of claudication nor the mechanism(s) by which exercise training improves walking times in persons with IC are completely understood. It is unknown how long-term exercise training effects skeletal muscle or to what extent skeletal muscle abnormalities in PAD are reversible. Women have been largely underrepresented in mechanistic studies of IC and exercise training. There is an urgent need for clinical research directed towards defining the basis of the exercise training changes induced in PAD patients in order to: 1) provide insights into the general pathophysiology of the exercise impairment in PAD; 2) permit scientifically plausible and testable modifications to currently prescribed exercise regiments to better employ this critical therapeutic modality; and 3) identify novel targets from pharmacotherapy that are capable of inducing the repertoire of molecular responses induced by exercise training.

Reproductive Health/Developmental Biology

▶ Title: *Evidence-based Practice Report on Assisted Reproductive Technology* AHRQ
Study Type: Policy analysis
Award: $150,000

Increasingly, assisted reproductive technologies (ART) are being employed to overcome infertility. Based on current reports, there appears to be an association between ART and adverse outcomes related to infant and child health. A careful evidence-based practice report is needed in order to disentangle treatment and infertility effects, especially to address the unique methodological challenges that are specific to this area of research. It is fairly well documented that ART results in greater numbers of multiple-gestation pregnancies, but the underlying causes are not well understood. More careful measures are needed for such outcomes as perinatal morbidities, birth defects, and developmental disabilities.

▶ Title: *Protein Tyrosine Kinases in Leiomyomata Uteri* NICHD
P.I.: Jean Wang, Ph.D.
Institution: University of California–San Diego
Grant No.: 5RO1 HD046225-02
Study Type: Basic
Award: $75,000

In this application, the investigators propose that female sex hormones stimulate the expression and/or activation of protein tyrosine kinases to promote uterine cell proliferation and tumor

growth, and predict that inhibition of protein tyrosine kinases involved in the proliferation of uterine cells would halt the growth of uterine leiomyomata. This study will survey the expression and activity of protein tyrosine kinases in normal uterine myometrium and leiomyoma specimens procured from women in different ages and racial/ethnic groups. The investigator plans to create a microarray that is suitable for profiling the expression of all 90 human protein tyrosine kinase genes. A strength of the application is the creation of the microarray, which is important and promises to have wide-scale application beyond the study of uterine leiomyomata. Results from this study may identify protein tyrosine kinases that are important for proliferation of uterine leiomyomata.

▶ Title: *Finding Genes for Uterine Fibroids* NICHD
P.I.: Cynthia Morton, Ph.D.
Institution: Brigham & Women's Hospital, Boston, MA
Grant No.: 1RO1 HD046226-02
Study Type: Translational
Award: $75,000

Although the majority of uterine leiomyomata are karyotypically normal, cytogenetic abnormalities are found in 25 to 40 percent of the tumors. This application proposes to perform a genome-wide scan to identify genes that predispose women to develop uterine leiomyomata and examine the relationship between genes that are involved in the pathogenesis of uterine leiomyomata. In an overall effort to understand the genetic contributions to the etiology, growth, and natural history of these tumors, correlation of genetic data from the genome-wide scan with environmental factors is planned. A strength of the application includes the recruitment and enrollment plan that is comprehensive with a special emphasis on African American women, the most severely affected segment of the population. This well-written study may facilitate understanding of the genetic pathways involved in the formation of uterine leiomyomata, which may ultimately lead to improved treatment options for affected women.

▶ Title: *Estrogen Dependency of Uterine Leiomyoma* NICHD
P.I.: Ayman Al-Hendy, M.D., Ph.D.
Institution: University of Texas Medical Branch, Galveston
Grant No.: 5RO1 HD046228-02
Study Type: Basic
Award: $75,000

The hormone-dependent phenotype of uterine leiomyomata suggests that interventions targeting the estrogen receptor-signaling pathway may have therapeutic efficacy. This Request for Applications plans to investigate the immune response and safety of single versus repeated recombinant adenovirus treatment alone or in combination with a selective estrogen receptor modulator (SERM) in mice, rat, and human leiomyoma cells. The strength and overall conceptual framework of this work is to test the validity and regulatory mechanisms of gene therapy as an alternative to non-surgical treatment for uterine leiomyomata, as well as to further elucidate the molecular mechanisms of estrogen dependency of uterine leiomyomata. This highly innovative research will add to our understanding of the molecular mechanisms of estrogen dependence in this common uterine tumor and may open a new area of investigation and treatment of uterine leiomyomata.

▶ Title: *Molecular Etiology of Leiomyoma Uteri* NICHD
P.I.: Cheryl Walker, Ph.D.
Institution: University of Texas MD Anderson Cancer Center, Houston
Grant No.: 1RO1 HD046282-02
Study Type: Basic
Award: $75,000

The goal of this application is to address the molecular regulation of uterine leiomyomata by identifying the mechanisms responsible for differential cell cycle regulation in uterine leiomyomata that may underlie inter-tumor heterogeneity and responsiveness. The investigator proposes to examine whether a well-defined cascade of molecular and genetic events in an identified tumor suppressor gene plays a role in estrogen receptor signaling and cell cycle control in rat and human leiomyoma cells. Strengths of this application include its sound and well-integrated specific aims. Results generated from these experiments may help elucidate how defective cell cycle regulation and estrogen receptor signaling contribute to the pathophysiology of uterine leiomyomata. This study may further advance our current understanding of the molecular mechanisms that play a role in the etiology and phenotypic heterogeneity observed in these tumors.

▶ Title: *Regulation of Uterine Fibroids by CCN5* NICHD
P.I.: John Castellot, Ph.D.
Institution: Tufts University School of Medicine, Boston, MA
Grant No.: 1RO1 HD046251-02
Study Type: Basic
Award: $75,000

This application proposes a research project that will elucidate the cellular, molecular, and biochemical mechanisms regulating the proliferation and motility of human uterine smooth muscle cells. The investigator has determined that estrogen induces a growth arrest-specific gene that inhibits motility and proliferation in cultured smooth muscle cells. This project will examine the pathophysiology of uterine leiomyomata from the point of view of specified gene interactions with estradiol and extracellular matrix. Strengths include the tightly focused and logical progression of experiments in animal models and human cells. Conceptually, the discovery of a gene as a mediator of estrogen-related regulation of uterine smooth muscle growth may help explain the estrogen sensitivity of uterine leiomyomata and provide a therapeutic basis for controlling formation and growth of these tumors.

▶ Title: *Reactive Oxygen Species Regulate Smooth Muscle Growth* NICHD
P.I.: Romana Nowak, Ph.D.
Institution: University of Illinois, Chicago
Grant No.: 1RO1 HD046227-02
Study Type: Basic
Award: $75,000

This application plans to investigate the key agents in the signaling pathway of smooth muscle cell proliferation that can be targeted by therapeutic agents. The investigator proposes that hormones related to obesity and hypertension, especially in African American women, may play a role in the pathogenesis of uterine leiomyomata. Animal models and human cell lines will be used in the study. A strength of the application is the novel hypothesis that uterine leiomyomata are a family of proliferative conditions, and that these tumors develop as a response to injury, particularly hypoxia; that oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy; and that proliferation is the result of growth factors, primarily, and steroid hormones, secondarily. Results obtained from this research may suggest a challenge to the existing paradigm that hormonal modulation is the key to development of uterine leiomyomata.

▶ Title: *Leiomyomata Uteri: Apoptosis and Cell Survival Pathways* NICHD
P.I.: Gregory Christman, M.D.
Institution: University of Michigan, Ann Arbor
Grant No.: 1RO1 HD046249-02
Study Type: Basic
Award: $75,000

This application proposes to study the effect of exposure to cytotoxic gene therapy, dietary estrogen alpha-receptor antagonist, and gonadotropin-releasing hormone agonist on leiomyoma cell proliferation and apoptosis in animal models and human cell lines. The overall hypothesis is that smooth muscle cell tumors have numerous cell-to-cell communications that make them uniquely susceptible to cell death via a bystander effect, which makes them a promising target for molecular therapy. Strengths of the application include its clinical relevance, the logical and innovative approach to developing novel therapeutic modalities, and verifying their effects on the molecular processes involved in cellular proliferation and apoptosis. Program staff will work with the applicant to address any identified weaknesses. Understanding the apoptosis and cell survival pathways active in uterine leiomyomata may allow the investigators to better promote long-term tumor regression in response to therapeutic agents.

▶ Title: *Estrogen Biosynthesis and Uterine Leiomyomata* NICHD
P.I.: Serdar Bulun, M.D.
Institution: University of Illinois, Chicago
Grant No.: 1RO1 HD046260-01
Study Type: Basic
Award: $75,000

In this application, the investigator proposes to determine the cellular and molecular mechanisms responsible for induction of normal and aberrant aromatase expression in uterine leiomyomata. The underlying rationale is underscored by the role of estrogen in the growth of uterine leiomyomata and the central role that aromatase expression plays in estrogen biosynthesis. The investigator plans to focus the investigation on the molecular mechanisms that may be involved in the induction of aromatase leading to estrogen biosynthesis within the myometrium/leiomyoma tissue. Major strengths of the proposal include the experience of the investigator and the well-developed experimental plan. Program staff will work with the applicant to address any identified weaknesses. Results obtained from this study may facilitate our understanding about how locally produced estrogen plays a critical role in the pathogenesis of uterine leiomyomata.

▶ Title: *Pregnancy and Drug Metabolizing Enzymes and Transporters* NICHD
P.I.: Steve N. Caritis
Institution: Magee-Women's Corporation, Pittsburgh, PA
Grant No.: 1 U10 HD047905-01
Study Type: Basic, clinical
Award: $350,000

The purpose of this research is to establish an Obstetric-Fetal-Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicant's OPRU. They will demonstrate their willingness to cooperate with other OPRUs to establish a network of OPRUs to identify and study common problems related to the use of pharmacologic agents during pregnancy. The investigators provide three protocols for assessment by the network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Women's Hospital) with more than 8,000 deliveries and a wide array of women with

medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expression, and sequencing endpoint measurements. A proteomics laboratory is also linked to the CCP. In addition to these clinical and analytical resources is a breeding rhesus monkey colony housed at Magee-Women's Hospital. A basic science component completes the Pittsburgh OPRU. A diverse group of basic scientists and clinical researchers has been interacting through the CCP and will add considerable breadth and depth to their OPRU. The leadership of the Pittsburgh OPRU provides a diverse and experienced group of researchers with a long history of collaboration and investigation in the area of maternal-fetal pharmacology. The leadership has experience in collaborative endeavors and is prepared to cooperate with other OPRUs to conduct collaborative research.

▶ Title: *Washington Obstetric–Fetal Pharmacology Research Unit* NICHD
P.I.: Menachem Miodovnik
Institution: Georgetown University, Washington, DC
Grant No.: 1 U10 HD047890-01
Study Type: Basic, clinical
Award: $150,000

The Washington Obstetric Pharmacology Research Unit (WOPRU) represents a collaboration among two universities and four medical centers in the nation's capitol that is uniquely positioned to use population pharmacokinetic, pharmacokinetic-pharmacodynamic, clinical trials simulation, and cutting-edge *in vivo* and *in vitro* techniques to assess clinical pharmacology of important therapeutic agents and their effects in pregnant women and their offspring. Specifically, the WOPRU combines the basic research resources of Georgetown University (lead agency) and George Washington University with the clinical strengths of MedStar Health (Washington Hospital Center and Georgetown University Hospital), George Washington University Hospital, and Children's National Medical Center. These hospitals are strategically placed throughout the DC metropolitan area, and are closely associated with the respective surrounding communities. The WOPRU obstetricians deliver over 7,000 babies from women who represent a broad spectrum of social, economic, ethnic, racial, and cultural backgrounds, with a large proportion of these pregnancies being high risk. The WOPRU institutions have an excellent track record of providing care and recruiting patients into clinical trials from this diverse community. The faculty of the WOPRU represent a team of highly motivated basic scientists and clinical investigators who are enthusiastically approaching the prospect of becoming a new center for OPRU. They are experienced investigators in a multitude of basic science and clinical disciplines with a unique combination of strengths in pharmacometrics, pharmacodynamics, pharmacogenetics, drug metabolism, therapeutic drug monitoring, proteomics, genomics, and biostatistics in conjunction with significant experience in multicenter clinical trials. The administration, and the basic science and clinical investigators of the WOPRU institutions, are unanimous in their eagerness to support and participate in the future OPRU network.

▶ Title: *University of Washington Obstetric–Fetal Pharmacology Research Unit* NICHD
P.I.: Mary F. Hebert
Institution: University of Washington, Seattle
Grant No.: 1 U10 HD047892-01
Study Type: Basic/Clinical
Award: $150,000

The overall objective of this research is to establish an Obstetric-Fetal Pharmacology Unit at the University of Washington. The major goal of the pharmacology unit will be to characterize the pharmacokinetics and pharmacodynamics of drugs that are of therapeutic value during pregnancy and whose clinical pharmacology is altered by the pregnant state. The general research focus will be cytochrome P450 enzymes and membrane transporters. There is an appropriate environment and resources at the University of Washington for establishing a successful and productive Obstetric-Fetal Pharmacology Research Unit. The following translational research studies that integrate the investigators strengths in clinical and basic sciences are proposed to evaluate the following study aims: 1) To determine whether the *in vivo* activities of CYP2C9 and organic cation transporter (OCT) are altered through stages of pregnancy using the phenotype markers, glyburide for CYP2C9 and metformin for OCT. Phase I (population pharmacokinetic analysis) and Phase II (pharmacokinetic /pharmacodynamic analysis) studies are proposed to investigate the effects of pregnancy on the aforementioned drug-metabolizing enzymes and transporters (second and third trimesters vs. 3 months postpartum period). 2) To determine the efficacy and safety of insulin vs. glyburide vs. glyburide plus metformin for treatment of gestational diabetes mellitus. A Phase III efficacy and safety trial is proposed to evaluate the effects of gestational diabetes, as well as the treatments on maternal, fetal, and infant/child developmental outcomes.

▶ Title: *Obstetric–Fetal Pharmacology Research Units Network* NICHD
P.I.: Gary D. Hankins
Institution: University of Texas Medical Branch, Galverston
Grant No.: 1 U10 HD047891-01
Study Type: Basic/clinical
Award: $150,000

The University of Texas Medical Branch (UTMB) will participate as a member of the Obstetric-Fetal Pharmacology Research Units (OPRU) Network. The principal investigator is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. Over 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The investigators have expertise in utilizing human placenta and derived preparations in the investigations and in placental receptors, their natural ligands and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They have investigated the effects of *in vitro* and *in vivo* chronic administration of opiates on placental physiology and maternal-neonatal outcome. Utilizing dual perfusion of placental lobule, they demonstrated the influence of efflux protein and placental metabolic enzymes on the PK for placental transfer of opiates. They identified placental aromatase as a drug-metabolizing enzyme and are investigating its polymorphism. One of the investigators is responsible for coordinating the baboon studies to be conducted at the Southwest National Primate Research Center in San Antonio. A population of normal and diabetic baboons will be studied. The Department of Ob/Gyn has scientists with expertise in areas relevant to this Request for Applications, including infection, vascular physiology, and placental functions. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

▶ Title: *Regulation of the Contraction in Human Uterus* NICHD
P.I.: Victor Fomin, Ph.D.
Institution: Indiana University School of Medicine, Indianapolis
Grant No.: 1 R03 HD045802-01A1
Study Type: Basic
Award: $100,000

Preterm uterine contractions or insufficient contractile activity during labor result either in miscarriage or in emergency cesarean section. A proper understanding of the mechanisms of uterine contraction and its cellular regulation is essential in finding ways to treat these uterine functional pathologies. Although the mechanisms of uterine smooth muscle contraction are generally understood, the factors responsible for the initiation of labor and the mechanisms by which the uterus maintains its contractility during labor are largely unknown. A growing body of evidence suggests that protein kinase C (PKC) plays an important role in regulation of contraction in a number of smooth muscles. However, its role in regulation of myometrium (uterine smooth muscle) is still controversial. Experimental results show both stimulatory and inhibitory effects of PKC on myometrial contraction. This complex mode of PKC action on rnyometrium can be explained by diversity within the PKC family of proteins, consisting of 12 known isoenzymes (isoforms). The investigators recently showed that seven of the isoforms are expressed in human non-pregnant myometrium, while in late pregnancy two more, PKC I and PKC II, are expressed. They have also shown a progressive increase in PKCa expression during pregnancy. The investigators hypothesize that different isoforms of PKC play specific stimulatory or inhibitory roles in regulating contraction of human myometrium. Early in the contraction-relaxation cycle some PKC isoforms can stimulate contractile pathways, and later other isoforms can decrease the rate of contraction, thus contributing to the muscle relaxation. Firstly, individual PKC isoforms will be depleted in myometrial cell line and muscle strips of human pregnant myometrium using isoform-specific anti-sense oligodeoxynucleotides (ODN). Secondly, the impact of this procedure on the intracellular-free Ca concentration in the cell line and on the intracellular-free Ca and the contraction of the muscle strip will be elucidated by measuring these parameters in the cells and the muscle strip. Knowing a crucial role of intracellular Ca ([Ca2+) in uterine contraction, the effect of the PKC depletion on [Ca2+] force relationship will be analyzed. This will help to better understand how PKC affects the uterine contraction during pregnancy. Within the scope of this proposal the investigators will concentrate on elucidation of the role(s) of PKCa as the isoforms expressed differently in pregnancy.

▶ Title: *Molecular Mechanisms of Ovarian Follicular Activation* NICHD
P.I.: Joanne Fortune, Ph.D.
Institution: Cornell University, New York, NY
Grant No.: 1 R03 HD045815-01A1
Study Type: Basic
Award: $99,999

In female mammals most oocytes reside in primordial follicles in a resting stage. Little is known about the mechanisms that regulate the movement of these follicles into the growing pool (follicle activation). The pool of resting primordial follicles is a resource, as yet untapped, that could be exploited as a source of material to provide alternative methods for alleviating infertility in women and propagating valuable domestic animals and endangered species. It is likely that a delicate balance among various factors, both stimulators and inhibitors, regulates follicular activation and growth *in vivo*. To date, efforts to determine the signals that initiate follicle growth have consisted of testing individual "candidates" to determine if they promote or inhibit follicle activation. Although progress has been made using this approach, that progress has been slow. The investigators will develop a complementary approach, based on recent advances in molecular

techniques, to determine specific genes that are turned on or off during the activation of follicles. In *Specific Aim 1*, suppressive subtractive hybridization (SSH) will be used to test the hypothesis that specific genes are turned on (or off) during follicle activation. Candidate genes will be determined by comparing freshly isolated pieces of bovine ovarian cortex (highly enriched for primordial follicles) with cortical pieces cultured for 2 days (in which 90 percent of follicles have activated and become primary). Cattle provide an excellent model for human follicular development and SSH are ideally suited for the detection of rare and novel sequences in two closely related cell types/tissues. *Specific Aim 2* is designed to test candidate genes identified in Specific Aim 1 for a potential role in follicle activation by using *in situ* hybridization to localize differentially expressed sequences in freshly isolated vs. cultured bovine cortical pieces. At the end of 2 years, the investigators expect to have identified a number of candidate genes that will provide important clues to the genetic regulation of follicle activation. Elucidation of these fundamental mechanisms has practical implications for the development of new contraceptive technologies and alleviation of infertility.

▶ Title: *Role of Neutralizing Antibodies in Transmission of SHIV* NICHD
P.I.: Nancy L. Haigwood, Ph.D.
Institution: Seattle Biomedical Research Institute, Washington
Grant No.: 2 R01 HD038653-04A1
Study Type: Clinical
Award: $99,999

Maternal neutralizing antibodies (NAbs) may play a role in determining whether an infant becomes infected during mother-to-child transmission (MTCT). Higher levels of both autologous and heterologous NAbs are associated with non-transmission. Although single-dose or multiple-dose nevirapine has limited transmission dramatically, there is growing concern over the development and persistence of drug-resistant viruses in the infants that could limit future treatment, raising interest in testing vaccines or immunotherapies during the early breastfeeding period, when postpartum transmission risk is highest. The focus of this research is to expand on the findings of the investigators previous study. They established a perinatal SHIV transmission model in *M. nemestrina*, where they have observed extraordinary virus control in infected and exposed newborn macaques. This model allows a detailed analysis of transmitted variants, passive transfer of maternal IgG and NAbs, and the development of autologous *de novo* responses in newborns. The research will explore the role of pre-existing NAbs in limiting infection and facilitating *tie novo* antiviral immunity. The researchers hypothesize that the presence of moderate to high levels of NAbs (IgG), at the time of oral SHIV exposure, will limit infection or pathogenesis in newborns by reducing the infectivity or number of variants that are transmitted. To test this concept, they will challenge newborns orally with SHIV in the presence of NAbs that are closely matched to the challenge virus versus mismatched NAbs. They will compare the development of *de nova* responses to SHIV with responses to hepatitis B vaccine given to the infant macaques in the absence of passive immunity. Understanding the potential and limitations of natural immunity will aid in the conceptual and optimal design of vaccines and immunotherapies that can further limit MTCT. Research focus includes: 1) characterize the transmitted viruses and the *de novo* antiviral responses in exposed infants with highly controlled SHIV infection and determine their profiles of neutralization sensitivity and resistance to passively acquired maternal IgG; 2) test the antiviral effects of IgG (SHIVIG) as a model for maternal antibodies in limiting infection, by comparing neutralizing IgG matched to the challenge virus versus mismatched IgG with limited or no neutralizing activity against the challenge virus; and 3) determine whether the presence of neutralizing versus non-neutralizing IgG affects the magnitude or timing of *de novo* NAbs in infected infants. Investigate possible mechanisms of action in the development of accelerated NAb responses and other antiviral immune responses.

▶ Title: *Development and Differentiation in Reproductive Axis* NICHD
Cooperative Reproductive Sciences Research at Minority institutions
P.I.: Director–David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, GA
Co-director/Partner–Tony M. Plant, Ph.D., University of Pittsburgh, PA
Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA
Grant No.: 5 U54 HD41749-04
Study Type: Basic science, translational, clinical
Award: $250,000

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health. The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core: Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant; Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann; Grant No. 2–1U54HD41749-010002 (Role of Prohibition in Follicular Development), Winston E. Thompson; Grant No. 3–1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran; and Grant No. 4–1U54HD41749-010004(SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

▶ Title: *Intermediate Outcomes of Hysterectomy and Alternatives* AHRQ
P.I.: Miriam Kuppermann, Ph.D.
Institution: University of California–San Francisco
Grant No.: 5 R01 HS11657-03
Study Type: Outcome Research
Award: $250,000

The proposed application expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal uterine bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the proposed study are: 1) to determine whether and how intermediate-term (4 to 8 year) clinical and quality-of-life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) to develop predictive models of treatment choice and satisfaction from a broad array of domains. The proposed expansion of the existing study is motivated by two main factors. First, by increasing the size of our cohort by an additional 700 we will extend the mean duration of follow-up from 1.7 to 4.1 years, and we will obtain at least 4 years of follow-up data on over 976 women. The increased sample at 4 years will allow the investigators to accrue an adequate number of women undergoing hysterectomy and non-surgical treatments to support a statistically meaningful comparison. Because symptoms for women with noncancerous uterine conditions typically extend from the early 40s to menopause, including intermediate-term, providing useful information will help equip women and their physicians to make informed, shared decisions. Second, we will enhance our measures of sexual functioning, depression, and incontinence, and include assessments of newly available alternative treatments. These additions reflect changes in the understanding of the role of these factors in the management of non-cancerous uterine conditions since the inception of the original study. The results of this study are central to the long-term goal of improving decisionmaking in the management of non-cancerous uterine conditions.

The findings that emerge from the proposed study will be relevant to the development of evidence-based guidelines and the creation of decision-assisting tools to help women with non-cancerous uterine conditions make informed choices regarding their treatment during their decade of risk for hysterectomy.

▶ Title: *The Biologic Effects of Androgens in Men and Women* NICHD
P.I.: Shalender Bhasin, M.D.
Institution: Charles R. Drew University of Medicine and Science, Los Angeles, CA
Grant No.: 5 U54 HD041748-02
Study Type: Basic science, translational, clinical
Award: $200,000

The Drew Center would serve to strengthen an existing, established, investigative effort between Charles R. Drew University and UCLA. The role of testosterone in normal female physiology is poorly understood and this center would serve to increase knowledge of the characterization of this hormone in sexual function, body composition and strength, and cognitive ability in women. One project uses the model of hormone-deficient women. Randomized treatment with varying doses of testosterone is proposed to address these important biological questions. Another project will test the hypothesis that female patients with panhypopituitarism would benefit from physiological testosterone replacement. A third project will use an animal model to examine the genetic factors, beyond hormonal effects, that regulate sex differentiation between male and female brains. The fourth project focuses on androgen-dependent stem cell differentiation. Strengths of the center include the expertise and experience of the investigative team, its clinical approach to examine whether testosterone replacement in physiological range can produce meaningful improvements in quality of life, and its unique approach to investigating the molecular basis of sex differentiation.

▶ Title: *Meharry Medical College/Pennsylvania State University Cooperative Center for Research in Reproduction* NICHD
P.I.: Ponjola Coney, M.D.
Institution: Meharry Medical College, Nashville, TN
Grant No.: 5 U54 HD044315-02
Study Type: Basic science, translational, clinical
Award: $200,000

The Meharry Center would serve to facilitate the development of a reproductive science research center at Meharry Medical College through a strong collaborative partnership with Pennsylvania State University. Studies outlined in these projects will generate knowledge and assess outcomes across the lifespan of women of different ages and racial/ethnic groups, including: 1) the role of sex steroid hormones as determinants of bone mineral density in African American females; 2) the influence of oral contraceptives on the growth of uterine fibroids; and 3) the efficacy and safety of metformin and lifestyle factors in the amelioration of polycystic ovary syndrome (PCOS) and its symptomatology in both adolescent and adult females. The overall objective is to determine whether ovarian production of estrogens and progesterone differ among women of diverse racial/ethnic groups and whether these determinants are responsible for racial differences in several positive and negative health outcomes. Strengths of the center include the innovative aspects of the proposed projects, their experimental designs, and the comparisons of lifestyle interventions and therapeutic regimens.

▶ Title: *Collaborative Research Initiative* NICHD
P.I.: Linda C. Guidice, M.D., Ph.D.
Institution: Stanford University, Palo Alto, CA
Grant No.: U54 HD 31398-08
Study Type: Translational
Award: $150,000

Endometriosis is a benign, estrogen-dependent, gynecologic disorder that is clinically associated with pelvic pain and infertility and is diagnosed by direct visualization during surgery. Pelvic endometriosis, and thus eutopic endometrium (i.e., endometrium within the uterus), is presumed abnormal in women with the disease. The abnormality extends to uterine receptivity, supported by high implantation failure and poor pregnancy rates in IVF cycles in women with disease. Recently, using a global gene profiling approach, we identified candidate genes for uterine receptivity in normally cycling women without endometriosis, and in women with mild/moderate endometriosis, through a collaborative, multicenter study. The current collaborative research initiative will lay the foundation for clinical translation of the data collected to date, with the following goals: diagnosis of a receptive endometrium for fertility; diagnosis of a non-receptive endometrium in women with endometriosis and infertility; diagnosis of endometriosis; and diagnosis of the stage (severity) of endometriosis in the pelvis.

▶ Title: *Prevalence and Etiological Predictors of Vulvodynia* NICHD
P.I.: Bernard L. Harlow, Ph.D.
Institution: Brigham & Women's Hospital, Boston, MA
Grant No.: 5 R01 HD38428-05
Study Type: Clinical
Award: $100,000

Vulvodynia is a syndrome of unexplained vulvar itching, burning, and/or pain that causes major physical and psychological distress. It is a diagnosis of exclusion when vulvar discomfort becomes chronic over many months and the presence of any other remediable cause, such as infection or dermatitis, is ruled out. The two major subtypes of vulvodynia—generalized vulvar dysesthesia and vestibulodynia—are often misclassified. Few descriptive or etiologic epidemiological studies have been performed. Thus, the prevalence and incidence in the general population is unknown and no preventable exposures have been identified. A recent NIH sponsored consensus conference stressed the need to determine the prevalence of vulvodynia and conduct population-based observational studies to identify modifiable risk factors. The applicant has conducted a population-based prevalence survey in more than 400 women that achieved a 70 percent response rate and found that 18 percent of women reported a lifetime history of chronic vulvar symptoms that lasted 3 months or longer. Approximately 8 percent of all women surveyed were currently experiencing these symptoms. In addition, the applicant conducted a pilot case-control study of 31 women diagnosed with either dysesthetic vulvodynia or vestibulodynia, or a combination of the two within the last 5 years and compared them to 31 similarly aged health women identified from the general population. Cases were, on average, three times more likely to report medical treatments or surgical procedures for conditions that may have influenced perineal pain, or a greater frequency of condom use and use of talcum powder in the genital area that may have lead to mucosal abrasion and inflammation. A survey is being conducted on 16,000 women, 20 to 59 years of age, from the general population to estimate the age-specific prevalence of vulvodynia. From this sample, the applicant will identify 400 cases of vulvodynia, verified through a two-step screening process, and a sample of 400 frequency matched age and county of residence controls. Structured interviews will assess a wide spectrum of exposures related to trauma. A subsample of 80 cases and 80 controls will receive a clinical examination to confirm the presence or absence of

vulvodynia, and also will provide a vaginal lavage and vulvar swab specimen for the assessment of cytokines and the culturing of microbiological organisms. It is hypothesized that various types of vulvar trauma may precede the spontaneous and evoked vulvar pain experienced by women with vulvodynia, and that vulvodynia may be a variant of a specific type of Complex Regional Pain Syndrome that is consistent with sensory disturbances such as mechanical allodynia.

▶ Title: *Vulvodynia Prevalence and Efficacy of Four Interventions* NICHD
P.I.: Gloria A. Bachmann, M.D.
Institution: UMDNJ–RWJ Medical School, New Brunswick, NJ
Grant No.: 5 R01 HD40119-05
Study Type: Clinical
Award: $100,000

Vulvodynia is a complex, multifactorial chronic pain syndrome which is associated with significant distress and interpersonal. Vulvar vestibulitis and dyspareunia are two common, although not well-understood clinical components or sub-types of vulvodynia. Chronic vulvar pain is experienced by, according to recent surveys, about 10 to 15 percent of the female population between ages 18 and 80. Pathophysiologic findings have not been convincing for the role of any specific antibody or etiological mechanism, although several have been proposed including aberrant somatosensory processing in the peripheral or central inflammatory process. The epidemiology and predictors of vulvodynia have similarly not been well-articulated in the literature. One study suggested that the disorder may be largely limited to white, middle-aged women, although sampling and data gathering limitations cloud the assessment of these findings. Thirdly, many centers have begun emphasizing surgical treatments for vulvar vestibulitis, although these approach is rejected by one-third of women at the outset. The vestibulectomy procedure also leads to definite worsening of the condition in 10 percent of cases. This grant will propose to examine efficacy, outcomes, and cost-effectiveness associated with four non-surgical interventions for vulvodynia. In general, the women's Health Research Section of RWJMS is committed to offering minimally invasive services and treatments to a broad diversity of women in the central northeast region. The investigators previous experience, and that of the co-principal investigators, make this site uniquely well-prepared to offer a broad range of dissemination and educational experiences, both locally and nationally, in the final years of the grant cycle. The investigators plan to arrange and host an international consensus conference (something they have done twice recently in other areas of relevance), and to disseminate findings obtained from this and similar conferences broadly. They will also disseminate any questionnaires and treatment manuals developed in the context of this grant via website or other appropriate electronic or non-electronic form. The investigators will develop patient education and public information materials, which will also be distributed in the most accessible and least costly form. The ultimate goal is to share findings from this and related research with the broadest cross-spectrum of women that we can.

APPENDIX E

Ad Hoc *Trans-NIH Working Group for Research on Chronic Fatigue Syndrome*

Eleanor Hanna, Ph.D. *Chair*	ORWH
J. Terrell Hoffeld, Ph.D.	CSR
Richard Nahin, Ph.D.	NCCAM
John D. Harding, Ph.D.	NCRR
Denise Russo, Ph.D.	NIAAA
David M. Morens, M.D.	NIAID
Thomas Esch, Ph.D.	NIAID
Deborah N. Ader, Ph.D.	NIAMS
Susanna Serrate-Sztein, Ph.D.	NIAMS
Lynne M. Haverkos, M.D.	NICHD
John Kusiak, Ph.D.	NIDCR
Anne P. Sassaman, Ph.D.	NIEHS
Annette Kirshner, Ph.D.	NIEHS
Peter Muehrer, Ph.D.	NIMH
Matthew V. Rudorfer, Ph.D.	NIMH
Linda Porter, Ph.D.	NINDS
Martha L. Hare, Ph.D.	NINR
Carl E. Hunt, M.D.	NHLBI
Stephen S. Goldman, Ph.D.	NHLBI
Joyce Rudick	ORHW
Susan Solomon, Ph.D.	OBSSR
Rebecca B. Costello, Ph.D.	ODS

APPENDIX F

Ad Hoc *Tracking and Inclusion Committee*

2003 & 2004 List of Members

Office of the Director

Office of Research on Women's Health
Vivian Pinn (Co-Chair), Angela Bates, Lisa Begg, Joyce Rudick
Office of Extramural Research
Carlos Caban,* Viktoriya Anufriyeva, Maria Koshy
Office of Acquisition, Management and Procurement
Barbara Levy

National Cancer Institute
Margaret Holmes,* Marilyn Gaston, Kim Witherspoon, Lisa Krueger, Clarissa Douglass

National Eye Institute
Lore Anne McNicol,* William Darby, Donald Everett

National Heart, Lung, and Blood Institute
Carl Roth (Co-Chair),* Sharry Palagi, Barbara Liu

National Human Genome Research Institute
Bettie Graham,* Pam Sellman

National Institute on Aging
Miriam Kelty,* Karen Bashir, Kate Nagy

National Institute on Alcohol Abuse and Alcoholism
Dorita Sewell,* Carmen Richardson

National Institute of Allergy and Infectious Diseases
Diane Adger-Johnson,* Susan Schafer, Diane Yerg, Martin Gutierrez

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Madeline Turkeltaub,* Charisse Lamar

National Institute of Child Health and Human Development
Eugene Hayunga,* Sandi Delcore

National Institute on Deafness and Other Communication Disorders
Julie Gulya,* Lana Shekim

National Institute of Dental and Craniofacial Research
Richard Mowery,* Trenita Davis

National Institute of Diabetes, Digestive and Kidney Disorders
Patricia Robuck,* Lauren Meskill, Donna James

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee

2003 & 2004 List of Members (continued)

National Institute on Drug Addiction
Christie Baxter*

National Institute of Environmental Health Sciences
Martha Barnes*

National Institute of General Medical Sciences
Lori Burge,* Alison Cole

National Institute of Mental Health
Catherine Roca,* Pamela Wexler, Sue Kennel, Ernesto Marquez, Dawn Corbett

National Institute of Neurological Disorders and Stroke
Frances Yee,* Kristy Woolbert

National Institute of Nursing Research
Alexis Bakos,* Christine Shaw

National Library of Medicine
Dwight Mowery*

Warren G. Magnuson Clinical Center
Kim Jarema,* Dee Koziol

National Center for Complementary and Alternative Medicine
April Bowers*

National Center for Research Resources
Sheila McClure,* Delores Lee, Patricia Newman, Stephen Seidel, Louise Ramm

Fogarty International Center
Aron Primack*

Center for Scientific Review
Anita Miller Sostek*

Office of Intramural Research
Alan Sandler*

National Center for Minority Health and Health Disparaties
Ivy Chan*

National Institute of Biomedical Imaging and Bioengineering
Meredith Temple-O Connor,* Tinera Fobbs, Tony Demsey, Casey Goode

Division of Extramural Activities Support
Mary Lou Prince,* Dorothy Sanders

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee

APPENDIX G
Office of Research on Women's Health Special Projects

FY 2003 SPECIAL PROJECTS

▶ Title: *Human Papaillomavirus 16 Virus-like Particles Vaccine Trials* NCI
Award: $600,000
Contact: Allen Hildesheim, Ph.D., and Doug Lowy, M.D.
Division of Cancer Epidemiology & Genetics, National Cancer Institute

Cervical cancer is a leading cause of cancer death for women around the world, but now that research has revealed the role of the human papillomavirus (HPV) in the pathogenesis of this cancer, research is now making progress in ways to prevent cervical cancer. One such study has developed a virus-like particle (VLP) vaccine against HPVs with the long-term goal of preventing or eliminating cervical cancer through the prevention of the transmission of HPV. Clinical trials are being conducted to determine the effectiveness of this HPV-VLP-based vaccine in preventing a persistent infection with HPVs. Early clinical trials of the vaccine have been completed indicating that they are well tolerated and highly immunogenic. A large-scale efficacy trial in Costa Rica to assess the ability of the vaccine is the next step in providing a vaccine that can have a global impact on women's cancers.

Safety and immunogenicity (Phase I & II) trials, which have been generously supported by the ORWH, are now completed and have demonstrated that the HPV16 VLP vaccine is well tolerated and induces strong immunological responses, and that these immune responses are observed systemically and at the genital tract of vaccinated women. Results from parallel Phase IIb trials, conducted by Merck Pharmaceuticals and GlaxoSmithKline (GSK) Biologicals, further indicate that HPV-VLP-based vaccines protect against persistent type-specific viral infection. These results are highly encouraging and suggest that VLP-based vaccines are likely to provide protection against high-grade cervical neoplasia and cervical cancer. To follow-up on these promising findings, we plan to conduct a 12,000 to 15,000 woman Phase III, randomized, pivotal trial to address the question of whether HPV-VLP-based vaccination reduces the incidence of high-grade cervical neoplasia and cervical cancer and to further evaluate its safety profile. In addition, numerous other important objectives will be addressed in our Phase III trial, including evaluation of duration of protection, type specificity of protection, and the impact of vaccination on rates of colposcopic referral and treatment.

While our efforts to set up the infrastructure for this Phase III trial in Costa Rica have progressed well, difficulties in obtaining sufficient GMP-grade vaccine have delayed trial initiation. To address this problem, we recently entered into a Clinical Trials Agreement (CTA) with GSK to use their HPV16/18 VLP vaccine in our Costa Rican trial. This new partnership has the advantage of allowing results from our trial in Costa Rica to be used directly to petition the FDA for licensure of a vaccine for widespread use, while allowing the NCI to maintain autonomy in the conduct, analysis, and interpretation of the trial and its results.

Efforts are now underway to make the modifications necessary to our protocols and to our infrastructure in Costa Rica to allow us to use the GSK-HPV16/18 VLP vaccine in a pivotal Phase III efficacy trial in Costa Rica. It is anticipated that a final protocol will be submitted to the FDA before the end of this year, and that the Costa Rican trial will begin in the late Spring of 2004.

In parallel with our efforts to obtain GMP-grade material for our efficacy trial, we have initiated various ancillary studies in Costa Rica aimed at furthering our understanding of the natural history of HPV and cervical neoplasia, and our understanding of immune responses to HPV infection. This has been possible given the personnel and infrastructure in place in Costa Rica. To date, three studies have been performed: one aimed at understanding patterns of mucosal immunity during the menstrual cycle (N = 200 women); a second aimed at understanding recently observed increases in HPV prevalence among the elderly (N = 550 women); and a third to evaluate HPV infections in the genital tract of women after treatment for HPV-related cervical lesions (N = 500 women). Biological specimens collected from participants in these ancillary studies have recently arrived in the United States. It is expected that we will initiate testing of these specimens in the coming year, to permit assessment of virologic and immunologic parameters required to achieve the objectives summarized above.

Finally, in addition to the trial designed to evaluate the efficacy of the GSK HPV16/18 VLP vaccine, trials are planned in the United States to evaluate an HPV16 chimeric virus-like particle (cVLP) vaccine, with the goal of having therapeutic potential against prevalent HPV infection, in addition to preventing incident infection. To achieve this goal, the cVLP vaccine contains, in addition to L1, a fusion protein composed of three HPV16 viral proteins, L2, E7, E2, with mutational inactivation of the Rb binding site of E7 and the DNA binding site of E2. Pre-clinical data suggest that immune responses to E7 and E2 may confer therapeutic efficacy.

▶ Title: *Safe Motherhood Initiative: Pregnancy and Depression* AHRQ
Award: $10,000
Contact: Jacqueline Besteman, J.D., M.A., Director, EPC Program, CPTA

The ORWH funded the Safe Motherhood Initiative which is an interagency work group to focus on women's health before, during, and after pregnancy, while continuing to promote infant health. ORWH/NIH, HRSA, OPHS, NIMH, CDC, NICHD, SAMHSA, and AHRQ are members of this group. The group selected perinatal depression as an area to develop a prototype project for interagency collaborative effort. Perinatal depression is understood to encompass major depressive episodes that either begin before pregnancy and continue through at least some of the pregnancy or postpartum period, or have onset during pregnancy, within 1 month of delivery (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*), or within the subsequent 11 months. This disorder can have devastating consequences. Perinatal depression affects not only the women experiencing it, but also the women's children. The Safe Motherhood Group is planning a conference for 2004 to bring all stakeholders up to the same level of appreciation for the quality and strength of the evidence base and to debate and decide next steps, including research, to expand understanding of this underappreciated medical and social problem. For that conference, the RTI-UNC Evidence Based Practice Center (EPC) has conducted this feasibility study for a full systematic review of the epidemiology, screening, and treatment of perinatal depression. In this report, we document the likely size of the evidence base by key question and category of question and describe the quality and strength of that evidence base as reflected in the "best" articles and data available.

▶ Title: *Making an Informed Choice: Is Lumpectomy A Safe Option for Me?* NCI, AHRQ, OWH-DHHS, CPR
Award: $20,000
Contact: Diana Zuckerman, Ph.D., President, National Center for Policy Research for Women & Families

The ORWH funded the Making an Informed Choice: Is Lumpectomy A Safe Option for Me? to support the development of patient and provider education materials for women diagnosed with DCIS or LCIS; and to help ensure that patients and health care providers have accurate, up-to-date, unbiased information based on research that has been conducted on these conditions. The pioneering support provided by the ORWH will help provide the important foundation for this on-going public education and training initiative.

▶ Title: *Sister-to-Sister Foundation: Everyone Has a Heart Health Fair* NHLBI
Award: $20,000
Contact: Greg Morosco, Ph.D.

The Sister-to-Sister: Everyone Has A Heart Foundation was founded to increase awareness about heart disease as the number one killer of women and to encourage healthy lifestyles. It is the only national organization whose focus is on screening women for heart disease. Because of the lack of awareness among women about the seriousness of heart disease and the belief that women can modify, control, or treat their risk factors for this disease, the foundation's mission is: 1) to provide women with opportunities to be screened for early detection and treatment of heart disease; and 2) to educate women about prevention measures, including a healthy diet, regular exercise, stress management, and smoking cessation to reduce heart disease risk factors.

This past February, Sister-to-Sister launched its national campaign in four cities: Chicago, New York, Philadelphia, and Washington, DC. Health fairs, executive women's breakfasts, and community-based screening events were held in each city. As a part of its expansion strategy, Sister-to-Sister formed partnerships with a number of organizations to accomplish the campaign goals. The 2003 Woman's Heart Day national campaign partners were the American Heart Association, Bristol-Myers Squibb, *Woman's Day* magazine, and the Discovery Health Channel. In addition, we continued to receive strong support from our federal partners: the Office of Research on Women's Health, NIH; the National Heart, Lung, and Blood Institute, NIH; and the Office of Women's Health, DHHS.

Highlights of the campaign include: 1) more than 3,000 women received free heart health screenings; 2) over 3,500 women attended the health fairs; 3) U.S. Department of Health and Human Services Secretary Tommy Thompson proclaimed the third Friday in February as National Woman's Heart Day; 4) Sister-to-Sister conducted its second annual Capitol Hill screening event on February 11th, sponsored by Bristol-Myers Squibb, where nearly 200 people received free heart health screenings. The American Heart Association co-hosted the event; and 5) 160 million impressions were made during the 10-day campaign, including TV, radio, newspapers, websites, and direct mail promotions.

Media highlights include: 1) President Irene Pollin and spokesrobot Holly Heart made an appearance on the Today Show with Katie Couric and Matt Lauer. 2) Other national media coverage included a comprehensive article in *Woman's Day* magazine, a 1-hour program on the Discovery Health Channel, articles in the *Washington Times* and *Roll Call*, and coverage of the campaign by numerous TV and radio stations. The campaign was advertised on the marquee at Madison Square Garden in New York City and the PECO Building Crown Lights in Philadelphia.

The campaign banners in Penn Station remained on display for 30 days after the event. 3) The Sister-to-Sister website, *www.SistertoSister.org*, was redesigned and included event schedules for the campaigns in the four cities. Links to the Sister to Sister website were posted on at least 25 websites. 4) 140,000 Valentine's Day cards with local event information were distributed in the four cities by school children to their mothers on Valentine's Day. 5) Billboard, shelter, and transit ads promoted the campaign in Philadelphia and New York, NY. 6) Onsite television coverage of the campaign took place in Chicago and Washington, DC.

2003 Heart Health screening results include: a total of 3,175 women were screened in the four cities during the 2003 Woman's Heart Day Campaign. Findings for 2003 were similar to 2001 and 2002 screening results and continue to raise concerns. Thirty-four percent, or 1,072 women out of 3,175 screened, were discovered to be at high risk for heart disease. The average age was 46 years, and 30 percent of the women were postmenopausal. The ethnicity of the women was 45 percent African American, 33 percent Caucasian, 10 percent Hispanic, and 12 percent from other ethnic groups. Fifty-three percent of the women had borderline or high total cholesterol (22 percent high); nearly 40 percent of the women had high blood pressure. Blood glucose (non-fasting) was high in just over 6 percent of the women.

Three year campaign results include: the Woman's Heart Day Campaign has attracted over 10,000 women to the health fair events. We have screened 7,000+ women and reached close to 200 million individuals through our promotional activities. We have distributed 170,000 Valentine's Day card through school children to their mothers. Our screening results have consistently identified at least 30 percent of the individuals screened at high risk for heart disease. This powerful grassroots campaign is making a difference in the lives of working women!

▶ Title: *Governors' Spouses Initiative To Curb Underage Drinking* NIAAA
Award: $100,000
Contact: Suzanne S. Medgyesi-Mitschang, Ph.D.

The ORWH supported a Leadership to Keep Children Alcohol Free national initiative. This funding has enabled the initiative's momentum and has been a determining factor in attracting a new group of Governors' spouses to the project. Both individually and as a group, they have a deep commitment to women's and children's health issues with a clear indication that the initiative holds a high priority on the national women's health agenda. When the leadership initiative was launched in March 2000, it was the *only* nationwide effort aimed at the prevention of alcohol use by children 9 to 15 years of age. A key purpose of the initiative was to place childhood drinking prevention as a priority issue on the health agenda of the Nation and to prompt more research in that area. Highlights include:

- Since its launch, 45 Governors' spouses have participated in this national program. The current group of Governors' spouses includes two Lieutenant Governors (in states where the Governor is not married), three Federal judges, and five practicing lawyers.
- As state leadership has changed through elections, the leadership has been successful in retaining the commitment of the majority of outgoing Governors' spouses (11 out of 15) who have joined in an 11-member Emeritus Group that is pledged to work actively in behalf of the leadership at a national level.
- The leadership has been particularly successful in the past year in moving the childhood drinking issue onto the policy agenda of Congress, the DHHS, other Federal agencies, and the National Academies of Science.
- As a result of a briefing for Senator Frist by one of the Emeritus Group members, Theresa Racicot (former First Lady of Montana), the Senator agreed to hold hearings on the issue of childhood drinking. Attending that meeting were NIH Director Elias Zerhouni and NIAAA Director Ting-Kai Li.

- The leadership Governors' spouses have been responsible for initiating several meetings with the U.S. Surgeon General, Dr. Richard Carmona, to brief him on the childhood drinking issue.
- On April 28, the current co-chairs of the leadership initiative—Columba Bush (Florida), Lori Hauser Holden (Missouri), Mary Easley (North Carolina), Hope Taft (Ohio), and two Emeritus Group members, Theresa Racicot and Sharon Kitzhaber (former First Lady of Oregon)—met with Dr. Carmona to request that he agree to undertake a Surgeon General report on childhood drinking, only the second report on the alcohol issue since 1963. Dr. Carmona agreed to this request. Dr. Carmona also volunteered to partner with the leadership Governors' spouses in his "50 State/50 School" initiative.
- At a July 14th meeting convened by the leadership co-chairs and the NIAAA Director, Dr. Carmona officially agreed to a Call to Action on the issue of childhood drinking and identified NIAAA as the lead agency for this effort. Also attending that meeting were the Deputy Directors of SAMHSA and NHTSA.
- As a result of the activities of the Governors' spouses active involvement in the leadership initiative, the issue of early alcohol use by pre- and early adolescents is now also receiving more attention within the NIH. The NIAAA has recruited a new Associate Director whose major emphasis is upon the 9 to 15 age group. Also, NIMH, NICHD, and NIDA have been invited to participate in an Interagency Working Group along with SAMHSA, Indian Health Service, CDC, HRSA, NHTSA, OJJDP, and the Department of Education in preparation for the Call to Action.
- The leadership was also invited by the National Academies of Science to present testimony at its public hearing on November 19, 2002 during the deliberations of the Committee on Developing a Strategy to Reduce and Prevent Underage Drinking.
- Current and former Governors' spouses are actively engaged in informing Congressional leaders about the consequences of childhood drinking. They have conducted policy briefings for legislators and State cabinet members and created public service announcements and videos for dissemination within their states. Several spouses have sponsored statewide poster contests and secured outdoor billboard advertising space in their states for a statewide childhood drinking prevention campaign. Their outreach and education also extends to making presentations at national conferences of major national organizations.

Recommendations for the future include:

- Encourage the U.S. Surgeon General to use the "bully pulpit" of his office to sustain attention to the human, health, and economic costs associated with underage drinking.
- Actively engage in the development of a new Surgeon General report on childhood drinking prevention that will establish recommendations for the Nation on this issue and that will identify new areas of research for the NIH.
- Translate the commitment of Governors' spouses to the leadership initiative into ongoing attention by the National Governors Association to the issue of underage drinking.
- Place the underage drinking prevention issue upon the Domestic Policy Council agenda to accomplish the following:
  1) Use the Federal program development and budgeting process to promote better collaboration at the Federal and State levels across all entities with responsibilities for children, youth, and underage drinking; and
  2) Identify areas of research in which increased funding availability would lead to prevention or reduction of underage drinking.

A three part strategy will be developed: Part I: Survey to assess curricular coverage of women's health in colleges and schools of pharmacy; Part II: Analysis of adequacy of existing evidence-based resources and teaching materials; and Part III: Modular development of new materials for teaching health professions students and practitioners, including interdisciplinary education and practice activities.

▶ Title: *Changing the Face of Medicine* NLM
Award: $300,000
Contact: Patricia Tuohy, Health Exhibition Program, National Library of Medicine

Changing the Face of Medicine, an exhibition at the National Library of Medicine, celebrates the achievements of women in medicine since they first gained admission to American medical school 150 years ago. Elizabeth Blackwell (1821-1910) and the first generation of women physicians struggled for access to education, hospital internships, and medical societies. Since then, women have challenged racial prejudice and gender bias to gain the professional opportunities and recognition they deserve. Gradually, women from diverse backgrounds have carved out successful careers in every aspect of the medical profession.

Whether shaping public health policy for whole populations, or providing health care to patients within a small community, women have changed the face of medicine at every level. They have also expanded its scope, often focusing on the needs of underserved populations or the ways in which race and gender affect health and illness. In scientific research, medical practice, and the education of future physicians, women have made important contributions to the health and well being of everyone around the world.

It would be impossible to recognize the achievements and contributions of every woman physician. By examining the exhibition, one may find that the women physicians whose stories are represented are examples of the fuller fabric of women's contributions to medicine and their personal achievements in society.

The exhibition includes historic artifacts, textile displays, audiovisual presentations, and digital interactives that showcase physicians' life stories. The installation and the online exhibition provide rich career resources and educational information for young people who are interested in pursuing a career in science and medicine. Changing Faces of Medicine will open to the public on October 14, 2003 and will run through April 2, 2005.

▶ Title: *Analysis and Documentation of Women's Health-related Content in the Curricula in the Schools of Public Health* HRSA
Award: $35,000
Contact: Sabrina Mattoff

The ORWH provided funding to the Maternal and Child Health Bureau, HRSA, to support the analysis and documentation of women's health-related content in the curricula in the estimated 32 U.S. Schools of Public Health. The goals of this work will be to better understand the degree to which women's health issues are addressed within the public health school curriculum, including stand-alone women's health courses, as well as the integration of women's health in courses that are required for a masters-level degree; and to disseminate the findings to member schools in an effort to further inform faculty and curricular planners about sex and gender differences in public health training, policy, and research.

▶ Title: *Obstetrician–Gynecologist's Knowledge and Practice Patterns with Regard to Hormone Therapy* NHLBI, HRSA
Award: $35,000
Contact: Barbara Alving, M.D.

The ORWH supported the study, Obstetrician–Gynecologist's Knowledge and Practice Patterns with Regard to Hormone Therapy. The study will increase the knowledge regarding practice patterns of OB/GYNs with respect to hormone therapy, as well as how to manage it with regard to all the conditions that are impacted by this therapy—hot flashes, cancer, osteoporosis, heart disease, etc. Since this is an NIH institute-wide issue, all relevant ICs will be contacted who are interested/involved in research related to HT and their participation solicited.

In the first year, a survey instrument will be developed in consultation with the NHLBI. This survey will be sent to 5,000 randomly selected Fellows through letter mail and web-based postings. The initial mailing will take place in June of 2003, with repeat mailings to non-responders in July and August. Surveys returned by September 15, 2003 will be analyzed. The goal is to work toward a response rate of 60 to 65 percent. The results of this survey will serve as a baseline for monitoring our physicians' knowledge and treatment patterns. The survey instrument will consist of questions on physician knowledge regarding the scientific evidence relevant to HT, physician self-assessments of their qualifications and training, clinical vignettes that require more detailed answers regarding physician prescribing patterns for HT, and physicians' impressions of their patients' awareness and concerns regarding HT.

The contract was signed before the end of the fiscal year 2003. There were some modifications to the original plan, in that ACOG will now do four surveys in each of spring 2004, 2005, 2006, and 2007. This will provide two late post-E+P trial surveys which will also be a baseline for the E alone findings in 2005; and two post-E-alone surveys which will give immediate and later effects on practice knowledge, attitudes, and prescription behavior. Next steps are to get the OMB approval process going and to revise the questionnaire, but there is more time for that since the first survey is scheduled for April 2004.

FY 2004 Special Projects

Evaluation of the ORWH's First Ten Years

The ORWH underwent an evaluation to review the contribution that the office has made to fostering women's health research, facilitating career development of women scientists, and promoting awareness of women's health research through outreach since the ORWH's inception at the NIH through FY 2000. The following synopsis provides an overview of this important task.

Key Findings

The Office of Research on Women's Health (ORWH), the focal point for women's health research at the National Institutes of Health (NIH), played a major role in achieving a culture change at the NIH. This is the conclusion of a comprehensive evaluation of ORWH activities and achievements during the office's first 10 years (FY 1991–2000). The study, conducted by Carlyn Consulting, found there was an increased awareness of women's health across the various NIH Institutes and Centers (ICs), resulting in substantially more NIH funding for research on diseases, disorders, and conditions that affect women.

A major reason for the ORWH's success was its proactive approach throughout the decade in reaching out to a broad range of scientists, professional organizations, and advocacy groups to exchange information and solicit recommendations for achieving common goals. Altogether, the ORWH actively participated in over 1,700 program activities during the 10-year period, a noteworthy record for a relatively small program. ORWH activities included the following:

- Sponsoring or co-sponsoring nearly 250 research conferences, seminars, and workshops.
- Organizing 16 trans-NIH committees/task forces.
- Achieving consensus on a comprehensive NIH-wide research agenda on women's health and working closely with the different ICs to encourage them to support research on high-priority women's health topics.
- Co-funding over 1,000 NIH research studies and over 125 career development awards.
- Providing nearly $95 million to ICs to support research on high-priority topics.
- Launching five new NIH programs to address the numerous barriers faced by women pursuing biomedical careers.
- Supporting over 90 activities to help ensure that women and minorities are appropriately included as subjects in clinical research studies supported by the NIH.
- Developing and/or co-sponsoring over 120 scientific publications, policy documents, and educational programs to promote women's health research and career opportunities.

Given the ORWH's limited staff and budget, its strong emphasis on interdisciplinary collaboration was essential to its success. Achievements included the following:

- *A dramatic increase in NIH announcements to stimulate and expand research on women's health*. The number of Requests for Applications (RFAs) and Program Announcements (PAs) encouraging researchers to address women's health issues increased by 143 percent during the ORWH's first 10 years, much higher than the 20 percent overall increase in NIH announcements.
- *A substantial increase in NIH grant applications and awards involving women's health research*. Grant applications involving women's health increased by 48 percent, nearly twice the 25 percent overall NIH increase in applications during the period. Perhaps more importantly, grant awards in high-priority areas increased by 70 percent, substantially higher than the 56 percent overall NIH increase in grant awards. The greatest expansion was seen in women's health research in the following areas: cultural and lifestyle factors, breast cancer, adolescent health, HIV/AIDS, behavioral change and risk-taking behavior, violence, menopausal hormone therapy, and menopause (in general).

- *More women are applying for and receiving NIH research grants*. The number of grant applications submitted by women increased by 56 percent during the ORWH's first 10 years, much higher than the 18 percent increase in applications from men. Also, the number of grants awarded to women increased by 84 percent, compared to a 49 percent increase in awards to men. The percent of awards to female principal investigators (PIs) increased for every type of grant analyzed, including R01 and P01 grants. At the end of the decade, female applicants had approximately the same probability of success as male applicants, indicating there was no systemic bias against female applicants. However, despite all of these gains, only 25 percent of NIH grant applications were being submitted by female PIs and they were receiving only 23 percent of NIH grant awards.
- *Increased institutional commitment to women's health research*. The number of academic institutions with major NIH research and training centers involving women's health increased by 87 percent, from 15 to 28, during the 1990s.
- *Strong evidence that women and minorities are being appropriately included as subjects in clinical research supported by the NIH*. Substantial evidence was found that the ORWH's efforts and those of other NIH offices and ICs were effective in strengthening NIH's inclusion policy. By the end of the decade, nearly all grant applicants were complying with NIH's policy, and the number of NIH-supported studies that examined sex/gender or racial/ethnic differences in disease etiology and treatment increased from an average of 101 to 398 per year.

After reviewing the findings, the evaluation advisory committee concluded that major factors in ORWH's success were: 1) its strong emphasis on collaboration and strategic planning; 2) its steady focus on a broad-based NIH research agenda for women's health; and 3) its effective leveraging of funds. There was consensus that the ORWH's approach could well serve as a model for other interdisciplinary programs pursuing trans-NIH issues and goals.

While emphasizing that a great deal of progress had been made, the members of the advisory committee also felt that there was more work to be done. Creative approaches are especially needed to encourage more female investigators to apply for NIH grants. In addition, the increased knowledge about women's health problems and the multisystemic nature of many of the diseases affecting women has led to additional questions that need to be addressed. Continued state-of-the-art research is needed on all of the diseases, disorders, and conditions affecting women.

▶ Title: *Human Papillomavirus 16/18 Virus-like Particle Vaccine Trial in Costa Rica* NCI
Contact: Allan Hildesheim, Ph.D., and Douglas Lowy, M.D.
Award: $600,000

Cervical cancer is a leading cause of cancer death for women around the world, but now that research has revealed the role of the human papillomavirus (HPV) in the pathogenesis of this cancer, research is making progress in ways to prevent cervical cancer. One such study has developed a virus-like particle (VLP) vaccine against HPVs with the long-term goal of preventing or eliminating cervical cancer through the prevention of the transmission of HPV. Clinical trials are being conducted to determine the effectiveness of this HPV-VLP-based vaccine in preventing a persistent infection with HPVs. Early clinical trials of the vaccine have been completed indicating that they are well tolerated and highly immunogenic. A large-scale efficacy trial in Costa Rica, to assess the ability of the vaccine, is the next step in providing a vaccine that can have a global impact on women's cancers.

Safety and immunogenicity (Phase I & II) trials are now completed and have demonstrated that the HPV16 VLP vaccine is well tolerated and induces strong immunological responses, and that these immune responses are observed systemically and at the genital tract of vaccinated women. Results from parallel Phase IIb trials, conducted by Merck Pharmaceuticals and

GlaxoSmithKline (GSK) Biologicals, further indicate that HPV-VLP-based vaccines protect against persistent type-specific viral infection. These results are highly encouraging and suggest that VLP-based vaccines are likely to provide protection against high-grade cervical neoplasia and cervical cancer.

To follow-up on these promising findings, we plan to conduct a 12,000 to 15,000 woman Phase III, randomized, pivotal trial to address the question of whether HPV-VLP-based vaccination reduces the incidence of high-grade cervical neoplasia and cervical cancer and to further evaluate its safety profile. In addition, numerous other important objectives will be addressed in our Phase III trial, including evaluation of duration of protection, type specificity of protection, and the impact of vaccination on rates of colposcopic referral and treatment.

Finally, in addition to the trial designed to evaluate the efficacy of the GSK HPV16/18 VLP vaccine, trials are planned in the United States to evaluate an HPV16 chimeric virus-like particle (cVLP) vaccine, with the goal of having therapeutic potential against prevalent HPV infection, in addition to preventing incident infection. To achieve this goal, the cVLP vaccine contains, in addition to L1, a fusion protein composed of three HPV16 viral proteins, L2, E7, E2, with mutational inactivation of the Rb binding site of E7 and the DNA binding site of E2. Pre-clinical data suggest that immune responses to E7 and E2 may confer therapeutic efficacy. This trial will be underway as soon as GMP-grade cVLP vaccine is produced by the contractor.

FY 2004 Update: The trial was initiated in Guanacaste, Costa Rica this past summer. To date, over 1,000 women have been enrolled into the trial. No serious adverse events related to vaccination have been reported. Women enrolled in the trial are randomly assigned to receive three doses of either the GSK HPV16/18 VLP vaccine or a control vaccine. Hepatitis A was chosen as the control vaccine given the potential benefit it would confer in this population.

We expect to enroll approximately 12,000 women into the trial, which is expected to take approximately 16 months. Women will be followed for a period of 4 years from enrollment. In addition to their three visits for vaccination, women will be followed annually, at which time semi-automated Thinprep cytology will be performed to screen for cervical lesions. Abnormalities identified cytologically will be followed either by referral to our study colposcopist for evaluation and treatment or by accelerated screening (every 6 months), depending on the severity of the cytological finding. During the vaccination and follow-up phases of our trial, women will be actively followed for adverse events.

In addition to the main objective of determining whether the HPV vaccine is effective at preventing HPV infection and the development of high-grade cervical lesions, we believe that the trial will afford a unique opportunity for us to evaluate many other scientific issues related to the natural history of HPV infection and to vaccine-related responses.

▶ Title: *Safe Motherhood Initiative: Pregnancy and Depression* AHRQ
Award: $10,000
Contact: Jacqueline Besteman, J.D., M.A., Director, EPC Program, CPTA

ORWH funded the Safe Motherhood Initiative which is an interagency work group to focus on Women's health before, during, and after pregnancy, while continuing to promote infant health. ORWH/NIH, HRSA, OPHS, NIMH, CDC, NICHD, SAMHSA, and AHRQ are members of this group. The group selected perinatal depression as an area to develop a prototype project for interagency collaborative effort. Perinatal depression is understood to encompass major depressive episodes that either begin before pregnancy and continue through at least some of the pregnancy or postpartum period, or have onset during pregnancy, within 1 month of delivery (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*), or within the subsequent 11 months. This disorder can have devastating consequences. Perinatal depression affects not only the women experiencing it, but also the women's children. The Safe Motherhood Group is planning a

conference for 2004 to bring all stakeholders up to the same level of appreciation for the quality and strength of the evidence base and to debate and decide next steps, including research, to expand understanding of this underappreciated medical and social problem. For that conference, the RTI-UNC Evidence Based Practice Center (EPC) has conducted this feasibility study for a full systematic review of the epidemiology, screening, and treatment of perinatal depression. In this report, we document the likely size of the evidence base by key question and category of question and describe the quality and strength of that evidence base as reflected in the "best" articles and data available.

▶ Title: *Making an Informed Choice: Is Lumpectomy A Safe Option for Me?* NCI
Award: $20,000
Contact: Diana Zuckerman, Ph.D., President, National Center for Policy Research for Women & Families

The ORWH funded the Making and Informed Choice: Is Lumpectomy A Safe Option for Me? Meeting with NCI, AHRQ, OWH, and CPR to support the development of patient and provider education materials for women diagnosed with DCIS or LCIS; and to help ensure that patients and health care providers have accurate, up-to-date, unbiased information based on research that has been conducted on these conditions. The pioneering meeting will help provide the important foundation for this on-going public education and training initiative.

▶ Title: *Sister-to-Sister Woman's Heart Day*
Award: $20,000
Contact: Irene Pollin, M.S.W.

The Woman's Heath Heart Day Health Fair was held on February 20, 2004 at the MCI Center in Washington, DC. The Woman's Heart Day campaign objectives are the following: 1) establish Woman's Heart Day as a nationwide 2-month campaign during January and February, culminating with the health fair on the third Friday in February; 2) provide access for all women to free heart health screenings; 3) collect and publish data about the clinical results of women screened during the campaign; and 4) engage national and local employers in promoting the campaign among their employees and providing financial and in-kind support about the campaign through local and national media.

In addition to complimentary screenings, health fair events include: educational seminars led by nationally known experts and celebrities, as well as fitness, beauty, and cooking demonstration. These events empower women to take control of their heart health. When a woman gets a simple heart-health screening, she's taken the most important step toward preventing heart disease.

The Sister-to-Sister – Everyone Has A Heart Foundation was founded to increase awareness about heart disease as the number one killer of women and to encourage healthy lifestyles. It is the only national organization whose focus is on screening women for heart disease. Because of the lack of awareness among women about the seriousness of heart disease and the belief that women can modify, control, or treat their risk factors for this disease, the foundation's mission is: 1) to provide women with opportunities to be screened for early detection and treatment of heart disease, and 2) to educate women about prevention measures, including a healthy diet, regular exercise, stress management, and smoking cessation to reduce heart disease risk factors.

Women's Heart Day Campaign 2004

- U.S. Department of Health and Human Services Secretary Tommy Thompson proclaimed the third Friday in February as National Woman's Heart Day.
- 160 million impressions were made during the 10-day campaign, including TV, radio, newspapers, websites, and direct mail promotions.

Highlights of 2004 Campaign

More than 15,000 women attended the health fairs in six cities and 3,308 women received free heart health screenings. Sister-to-Sister conducted its third annual Capitol Hill screening event on February 10th, sponsored by Bristol-Myers Squibb, where nearly 700 people attended and 300 people received free heart health screening. Over 200 million media impressions were made during the campaign, including TV, radio, newspapers, websites, and direct mail promotions.

Media highlights included an article in *Working Mothers* magazine; PSAs run on the Discovery Health Channel and local news stations; articles in the *Washington Post*, *Philadelphia Tribune*, *Chicago Tribune,* and *Roll Call*, as well as coverage of the campaign by numerous television and radio stations. The Sister-to-Sister website was redesigned and included event information for the six cities. Links to the website were posted on at least 25 websites. Over 200,000 Valentine's Day cards with local event information were distributed in the six cities by school children to their mothers on Valentine's Day. Shelter and transit ads promoted the event in Washington, DC; the New York event was advertised on the marquee at Madison Square Garden. Out of the 3,308 women who were screened, 53.9 percent were discovered to have borderline or high total cholesterol. Nearly 42 percent had high blood pressure. Blood glucose (non-fasting) was high in just over 8 percent of the women. The average age was 47 years. The ethnicity of the women was 31.1 percent African American, 45.6 percent Caucasian, 6.7 percent Hispanic, and 16.6 percent from other ethnic groups

▶ Title: *Governors' Spouses Initiative To Curb Underage Drinking* NIAAA
Award: $100,000
Contact: Suzanne S. Medgyesi-Mitschang, Ph.D.

The ORWH supported A Leadership to Keep Children Alcohol Free national initiative. The ORWH's continued support has been extremely important to the leadership in continuing activity at both the state and national levels. Not only has your funding been crucial in sustaining the initiative's momentum, but it has also been a determining factor in attracting successive new groups of Governors' spouses to the project as elections and changes in Governorships take place. Both individually and as a group, Governors' spouses have a deep commitment to women's and children's health issues. The ORWH's participation is a clear indication to them that the initiative holds a high priority on the national women's health agenda.

- This year, the National Institute of Child Health and Human Development (NICHD) added its support to the Leadership initiative.
- Since its launch in March 2000, over 60 Governors' spouses have participated in the leadership initiative. At present, 32 current Governors' spouses are members of the initiative and there are 15 members of the Emeritus group.
- The leadership has established an independent 501c3 foundation—the leadership to Keep Children Alcohol Free Foundation. The Christopher D. Smithers Foundation has pledged substantial support to the leadership foundation.
- The leadership continues to play a critical role in moving the childhood drinking issue onto the policy agenda of Congress, the DHHS, and other federal agencies:
  - ▶ The Emeritus Group enlisted the support of Senators Kay Bailey Hutchison and Barbara Mikulski to sponsor legislation for a semi-postal stamp on childhood drinking. Legislation has been introduced in the Senate and it is hoped that it will yet pass during the current Congressional session (when Congress returns from its election recess).
  - ▶ Hope Taft (First Lady, Ohio) provided a statement for the *Congressional Record* submitted to the Subcommittee on Education Reform on behalf of the Leadership on February 11, 2004.

- Hope Taft also provided testimony at the Principals' meeting for the Interagency Coordinating Committee for the Prevention of Underage Drinking (ICCPUD). The formation of the ICCPUD was mandated by Congress for heads of Federal agencies to address underage drinking prevention.
- The leadership, in partnership with other organizations, provided support for the Sober Truth on the Prevention (STOP) of Underage Drinking Act introduced recently in both the Senate and House.
- Governors' spouses continue to be active in their states promoting childhood drinking prevention through a variety of outreach activities.
- Hold policy briefings for state agency representatives and other stakeholders. The Institute of Medicine's report has been used as a framework for various states to develop strategies to address underage drinking prevention.
- Smart and Sober Celebration in Ohio for over 6,000 5th through 8th graders.
- Mikey Hoeven (First Lady, North Dakota) is collaborating with the regional Applebee's to raise awareness and raise money for childhood drinking prevention activities.
- Participating Governors' Spouses engaged in the following activities in 2003: five briefings, 26 media/publicity appearances, 17 op-eds/articles published, two outreach campaigns to families, 33 outreach campaigns to state and local organizations, five outreach campaigns to national organizations, four outreach campaigns to parents, 14 outreach campaigns to youth, three youth poster contests, 24 presentations to the prevention community, and seven school visits.

- Title: *Changing the Face of Medicine* NLM
  Award: $300,000
  Contact: Patricia Tuohy, Health Exhibition Program, National Library of Medicine

Changing the Face of Medicine, an exhibition at the National Library of Medicine, celebrates the achievements of women in medicine since they first gained admission to American medical school 150 years ago. Elizabeth Blackwell (1821-1910) and the first generation of women physicians struggled for access to education, hospital internships, and medical societies. Since then, women have challenged racial prejudice and gender bias to gain the professional opportunities and recognition they deserve. Gradually, women from diverse backgrounds have carved out successful careers in every aspect of the medical profession.

Whether shaping public health policy for whole populations, or providing health care to patients within a small community, women have changed the face of medicine at every level. They have also expanded its scope, often focusing on the needs of underserved populations or the ways in which race and gender affect health and illness. In scientific research, medical practice, and the education of future physicians, women have made important contributions to the health and well being of everyone around the world.

It would be impossible to recognize the achievements and contributions of every woman physician. By examining the exhibition one may find that the women physicians whose stories are represented are examples of the fuller fabric of women's contributions to medicine and their personal achievements in society. The exhibition includes historic artifacts, textile displays, audiovisual presentations, and digital interactives that showcase physicians' life stories. The installation and the online exhibition provide rich career resources and educational information for young people who are interested in pursuing a career in science and medicine. Changing Faces of Medicine will open to the public October 14, 2003 and will run through April 2, 2005.

▶ Title: *Analysis and Documentation of Women's Health-related Content in the Curricula in the Schools of Public Health* — HRSA
Award: $35,000
Contact: Sabrina Mattoff, HRSA

The ORWH provided funding to the Maternal and Child Health Bureau, HRSA, to support the analysis and documentation of women's health-related content in the curricula in the estimated 32 U.S. Schools of Public Health. The goals of this work will be to better understand the degree to which women's health issues are addressed within the public health school curriculum, including stand-alone women's health courses, as well as the integration of women's health in courses that are required for a masters-level degree; and to disseminate the findings to member schools in an effort to further inform faculty and curricular planners about sex and gender differences in public health training, policy, and research.

▶ Title: *Obstetrician–Gynecologist's Knowledge and Practice Patterns with Regard to Hormone Therapy* — NHLBI HRSA
Award: $35,000
Contact: Barbara Alving, M.D.

The ORWH supported the study, An Obstetrician-Gynecologist's Knowledge and Practice Patterns with Regard to Hormone Therapy. The study will increase the knowledge regarding practice patterns of OB/GYNs with respect to hormone therapy (HT), as well as how to manage it with regard to all the conditions that are impacted by this therapy—hot flashes, cancer, osteoporosis, heart disease, etc. Since this is an NIH institute-wide issue, all relevant ICs will be contacted who are interested/involved in research related to HT and their participation solicited.

In the first year, a survey instrument will be developed in consultation with the NHLBI. This survey will be sent to 5,000 randomly selected Fellows through letter mail and web-based postings. The initial mailing will take place in June of 2003, with repeat mailings to non-responders in July and August. Surveys returned by September 15, 2003 will be analyzed. The goal is to work toward a response rate of 60 to 65 percent. The results of this survey will serve as a baseline for monitoring our physicians' knowledge and treatment patterns. The survey instrument will consist of questions on physician knowledge regarding the scientific evidence relevant to HT, physician self-assessments of their qualifications and training, clinical vignettes that require more detailed answers regarding physician prescribing patterns for HT, and physicians' impressions of their patients' awareness and concerns regarding HT.

The contract was signed before the end of the fiscal year 2003. There were some modifications to the original plan, in that ACOG will now do four surveys in each of spring 2004, 2005, 2006, and 2007. This will provide two late post-E+P trial surveys, which will also be a baseline for the E alone findings in 2005, and two post-E-alone surveys that will give immediate and later effects on practice knowledge, attitudes, and prescription behavior. Next steps are to get the OMB approval process going and to revise the questionnaire, but there is more time for that since the first survey is scheduled for April 2004.

APPENDIX H
Office of Research on Women's Health Conferences and Workshops

ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2003

▶ Title: *Diabetes Town Meeting* DHHS
Award: $5,000
Contact: Frances E. Ashe-Goins

The Diabetes Town Meeting was held in Washington, DC, May 20, 2003. Major objectives of this meeting included: providing accurate, up-to-date health information on diabetes to women; educating women about their risk for diabetes with prevention and management approaches; fostering development and support of diabetes control programs for women; showcaseing national and community resources for women and diabetes; and encouraging the establishment of networks for interaction, information, and community action on diabetes prevention and treatment.

▶ Title: *Vulvodynia—Toward Understanding a Pain Syndrome Workshop* NICHD
Award: $5,000
Contact: Marianne Glass Duffy

This workshop was held April 14-15, 2003 at the Lister Hill Auditorium at the NIH. The aims of this workshop were: 1) to present an overview of the science and epidemiology of vulvodynia; 2) to elucidate the fundamental mechanisms of vulvodynia and related pain syndromes; 3) to stimulate innovative research approaches to vulvodynia; and 4) to develop clinical strategies for the appropriate and evidence-based methods of alleviating vulvar pain.

▶ Title: *Basic Science—Translational and Clinical Disease in Female Pelvic Floor Disorders Conference* NICHD
Award: $5000
Contact: Anne M. Weber, M.D., M.S.

This conference was held on November 15-16, 2002 in Bethesda, Maryland. Major objectives to be discussed included: the review and brief report on current research; the use of different mechanisms depending on specific needs; the terminology and continuing need for standardization; the need for research and training; and the need for developing a research agenda in female pelvic floor disorders for the next 5 years.

▶ Title: *ADD Health Users Conference* NICHD
Award: $5,000
Contact: Christine Bachrach, Chief, Demographic & Behavioral Science Branch

The ADD Health Users Conference was held in Bethesda, Maryland, on July 28-29, 2003. These conferences provide an opportunity for investigators using the ADD Health data to share research findings, discuss issues in the analysis of this complex data set, and learn about specializes aspects of the data and its use. This conference consisted of three types of sessions: paper sessions, didactic sessions, and "special" sessions focusing on how to talk to the press for young investigators.

▶ Title: *Vitamin D and Health in the 21st Century: Bone and Beyond* NICHD
Award: $5,000
Contact: Daniel Raiten, Ph.D.

This conference was held on October 9-10, 2003 in Bethesda, Maryland. Highlights of the agenda include: demographics and methodology of epidemiology, the current understanding of the role of vitamin D in health and potential mechanisms for vitamin D-related diseases, and developmental, ethnic/racial considerations in generating recommendations for vitamin D.

▶ Title: *FASEB Autoimmunity Conference* NIAID
Award: $5,000
Contact: Lawrence J. Prograis, Jr., M.D

This conference was held June 28-July 3, 2001 in Saxtons River, Vermont. The goal of this meeting was to help establish and maintain communication between scientists of diverse backgrounds who share common interest in autoimmunity. The conference proved to be highly informative. Much of the data presented was unpublished, thus providing attendees with the most up-to-date knowledge of this fast-moving field.

▶ Title: *Outcome Measures for Sjögren's Syndrome Workshop* NIDCR
Award: $5,000
Contact: Kevin Hardwick

The conference covered definitions and identification of Sjögren's syndrome, outcome measures, quality of life, clinical trials, serial biopsies and focus scores, additional outcome measures that have already been used in clinical trials, and an open forum to discuss individuals' outcome measures that have not already been proposed.

▶ Title: *American Society for Cell Biology Annual Meeting*
Award: $3,000
Contact: Ms. Elizabeth Marincola

This meeting was held December 14-18, 2002 in San Francisco, California. The Office of Research on Women's Health has supported the 41st annual meeting. These funds supported costs for the Women in Cell Biology and Education Committees Career Discussions and Networking Program. Roundtable discussions were lead by women leaders in molecular biology and other related fields of biomedical research.

▶ Title: *Fourth International Symposium on Hormonal Carcinogenesis* NCI
Award: $5,000
Contact: Karen Grotzinger

This symposium was held June 21-25, 2003 in Valencia, Spain. The goal of the symposium was to focus on major developments in the rapidly expanding field of hormonal carcinogenesis and hormonal cancers. A novel format for these symposia was used to integrate different disciplines and approaches in each of the sessions to include basic science, epidemiologic, and clinical research. Each session focused on a specific aspect of a prevalent hormone-related cancer. Information gathered from cell-free systems, cell cultures, animal models, and human studies, together will provide important insights to our understanding of hormonal cancer causation, development, and prevention—the primary objective of these symposia.

▶ Title: *Women, Tobacco, and Cancer: An Agenda for the 21st Century* NCI
Award: $10,000
Contact: Anna T. Levy

This meeting was held in Houston, Texas, February 3-5, 2003. Major conference goals include: 1) identify and prioritize research needs to increase understanding of cancer-related biological effects on women's tobacco use and environmental tobacco smoke (ETS) exposure; and 2) develop better interventions to decrease women's and girls' tobacco use exposure. In addition, research areas highlighted the biology of addiction, cancer susceptibility, behavioral aspects of tobacco use, and communications and intervention work.

▶ Title: *Parenthood after Cancer: Today's Options and Tomorrow's Hopes* NCI
Award: $5,000
Contact: Anna T. Levy

This conference was held March 5-7, 2004 at the Hickey Auditorium, University of Texas M.D. Anderson Cancer Center, Houston. The purpose of this conference was to convene the first international meeting on fertility and pregnancy after cancer, and the genetic consequence of cancer treatment on offspring born to cancer survivors. This conference included advances in fertility preservation, infertility treatment, and the impact of cancer treatment on pregnancy. Also included were communicating fertility risks and options to cancer patients and their partners, and the psychosocial aspects of choosing nonbiological parenthood among cancer survivors.

▶ Title: *Computer-based Technology and Caregiving of Older Adults* NIA
Award: $5,000
Contact: Dr. Sydney Stahl

The conference was held in the Natcher Center at the National Institutes of Health, October 2-3, 2003. The purpose of this conference was to elevate awareness in the family caregiving community throughout the United States to the rapidly increasing importance of computer-based technology in helping support quality caregiving for older Americans. A press release follows.

▶ Title: *National Meeting on Treatment Options for LCIS and DCIS*
Award: N/A
Contact: Diana Zuckerman, Ph.D.

The conference was held on September 22, 2003 at the National Institutes of Health. The purpose of this working conference was to bring together a dozen of the foremost experts on DCIS and LCIS, to determine what consensus there is about treatment recommendations, and what information could be provided to patients in booklet form.

▶ Title: *Workshop on Phenotyping Obesity for Human Genetic Studies* NIDDK
Award: $5,000
Contact: Robert Karp, Ph.D.

It is widely accepted that identification of genes predisposing to obesity in humans would lead to great advances in understanding of the physiology of obesity, and provide leads for the development of interventions to prevent and treat this increasingly prevalent disorder. It appears that gene identification will require larger-scale studies, which classify individuals into phenotypically homogeneous groups at a greater level of physiological detail than previous studies have attempted. The purpose of this workshop will be to consider a wide range of anatomical, physiological, behavioral, and developmental phenotypes relevant to obesity and its major medical consequences, and to recommend a comprehensive set of biologically informative, cost-effective measurements to be incorporated into the design of a large-scale genetic study of obesity.

▶ Title: *Environmental Factors in Autoimmune Disease* NIEHS
Award: $5,000
Contact: J. Patrick Mastin, Ph.D.

The purpose of this workshop was to explore the role that exposures to environmental agents play in the development and exacerbation of autoimmune diseases. The goals were to get input from the environmental health science and autoimmune research communities on the most appropriate and productive directions for research.

▶ Title: *A Multicultural Caribbean United Against HIV/AIDS* OAR
Award: $200,000
Contact: Jack Whitescarver, Ph.D.

This was a unique forum and opportunity to disseminate information to those critically impacted by HIV/AIDS, many of whom are women. The conference goals were: 1) to enhance the Caribbean's regional efforts to work collectively towards preventing the spread of HIV and mitigation of HIV/AIDS' impact on the health, social, and economic status of the region; 2) to improve regional responses to HIV/AIDS through the application of knowledge, research, learning, collaboration, and best practices within the Caribbean region; and 3) to develop the regional research capacity through the promotion of a Caribbean research agenda on HIV/AIDS and the dissemination of the latest HIV/AIDS research information.

▶ Title: *Health Issues and Concerns of Women of Color*
Award: N/A
Contact: Celia Maxwell, M.D.

This conference addressed A Call to Action IV: HIV, STDs and Women: Still a Challenge. Issues addressed included STDs, HIV, pregnancy, complimentary and alternative medicine, and the importance of mental wellness.

ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2004

▶ Title: *Preventing Suicide* NIMH
Award: $5,000
Contact: Cathy Roca, M.D.

The central theme of the series was the integration of public health-oriented prevention efforts and clinical interventions to reduce the frequency of suicide and serious attempts in critical populations—youth and young adults, elders, men in their middle years, and women. There was an emphasis on translating the findings from risk factor research into practical methods of prevention, with an evidence-based approach to the evaluation of these interventions.

▶ Title: *2004 Minority Women's Health Summit* OWH
Award: $20,000
Contact: Francis Ashe-Goins

This conference built on the outcomes of the 1997 National Conference, Bridging the Gap: Enhancing Partnerships to Improve Minority Women's Health. Key areas in women's health, including cardiovascular disease, cancer, diabetes, and HIV/AIDS, were highlighted.

- Explore current prevention strategies that work in various communities, both urban and rural.
- Promote dialogue among policy makers, service providers, community women, academia and other stakeholders to address current health care issues for women of color.
- Recommend action-oriented strategies to increase positive health outcomes for women of color across the life span, from rural and urban communities.
- Foster community partnerships to identify and implement best practices that target prevention, diagnosis, and treatment of diseases that disproportionately affect women of color.
- Promote strategies to diversify leadership in health sciences, education, research, and policy.
- Ensure health issues of women of color remain at the forefront of national, state, and local health policy agendas.

▶ Title: *Elders' Oral Health Summit* NIDCR
Award: $2,500
Contact: Pat Bryant, Ph.D.

This workshop, scheduled for September 2004, examined elders' access to dental care in the United States and abroad, and compare options for improving access and oral health outcomes in the elderly.

▶ Title: *Estrogen as a Case Study* NIA
Award: $5,000
Contact: Marilyn Miler, Ph.D.

This 2-day workshop, held September 28-29, 2004, brought together scientists in the fields of basic science, reproductive epidemiology, and clinical trials. The focus of the workshop was on the presentation of data in hand to determine why the Women's Health Initiative gave different results than predicted from basic and epidemiological studies. Information presented at this workshop aided in the consideration of whether future epidemiological studies and clinical trials should take place and if so, how they should be planned.

▶ Title: *2004 Reproductive Tract Biology Gordon Conference* NICHD
Award: $5,000
Contact: Diane F. Alexander, M.D.

The Reproductive Tract Biology Gordon Conference was held in June 2004. The nature of focuses on the biology, and the pathology of the organs and organ systems of the male and female reproductive tracts, rather than on specific molecules or processes and on breast cancer. Accordingly, the principal goal of this conference was to stimulate cross-disciplinary exchange and integration of information concerning the reproductive tract and mechanisms associated with normal and pathological processes in the mammary gland. Three specific aims were: 1) the scientific content of the meeting will be at the highest level. To achieve this standard of excellence, speakers who are internationally recognized experts at the forefront of there fields were invited; 2) there was a strong emphasis on research that is highly relevant to important clinical questions and has potential for translation into medical practice; and 3) there was a strong emphasis on the inclusion of students and junior colleagues as the future of any field depends on the next generation of investigators.

▶ Title: *John Diggs Lecture Speaker* OIR
Award: $200
Contact: George M. Langford, Ph.D.

This lecture was held in July and featured a keynote speaker. The title of the lecture was Molecular Motors and Memory: Building a Careers in Biomedical Science and the S&E Workforce.

▶ Title: *5th Annual ADD Health Workshop* NICHD
Award: $2,500
Contact: Dr. Christine Bachrach

This workshop focused on presentations of current findings and training for future research using the National Longitudinal Study of Adolescent Health (ADD Health) data set. In July, the NICHD hosted a group of approximately 150 faculty, graduate students, and researchers for the fifth annual ADD Health Users Group Workshop.

▶ Title: *African American Bioethics Conference* NIAID
Award: $15,000
Contact: Dr. James P. Comer

This conference was held in September 2004. The purpose was to discuss the culture of ethics and determine potential impact in the role of gender and clinical research in the African American community.

▶ Title: *Reproduction and the Fragile X Permutation Conference* NICHD
Award: $5,000
Contact: Lawrence Nelson, M.D.

This workshop, which will be held in FY 2005, will focus on questions regarding the impact of the fragile X premutation on reproduction; define the research gaps, needs, and opportunities; and make recommendations on what the NIH can do to move this research agenda forward. The purpose of this conference is to examine the basic science, clinical, and epidemiological evidence regarding the fragile X premutation and its effects on reproduction. Gaps in existing knowledge will be defined and strategies to address these gaps will be developed. The fragile X premutation presents multidisciplinary problems that will require us to bring together diverse expertise. The meeting will bring together epidemiologists, geneticists, genetic counselors, gynecologists, internists, family physicians, endocrinologists, neurologists, clinical investigators, and basic scientists.

▶ Title: *AAOS Symposium on the Influence of Sex Specificity and Gender on Musculoskeletal Health* NIAMS
Award: $5,000
Contact: Robin Strachan

The purpose of this symposium and subsequent publication is to bring to the orthopedic field the advances that has been made in the understanding of how female biology and physiology impact on musculoskeletal health by bringing basic scientists and engineers together with clinicians who treat the musculoskeletal patient at all stages of their care. Furthermore, the symposium identified new areas of research related to sex and gender issues in musculoskeletal health.

▶ Title: *Biology of the Perimenopause* NIA
Award: $5,000
Contact: Sherry Sherman, M.D.

This 1 1/2-day workshop was held in May 2004 in Bethesda, Maryland. It brought together experts to summarize ongoing and previous clinical, molecular, and cellular studies related to H-P-O axis function in premenopausal, perimenopausal, and postmenopausal women and relevant animal models that relate to increased risk of health problems and conditions associated with the menopause, and to identify future research studies needed to fully explore the biology of premenopausal protection.

▶ Title: *Hot Flash Measurement Workshop* NCCAM
Award: $10,000
Contact: Heather Miller, Ph.D.

In collaboration with the ORWH and other NIH ICs, NCCAM convened a 1-day workshop to assess existing measures of hot flashes and to determine how measures could be improved. Improved objective measures of hot flashes could be used to assess and improve the quality for self-reported data. The workshop resulted in a paper summarizing those deliberations and perhaps an NIH initiative in this area.

▶ Title: *Long-term Follow-up of Prenatal Drug Exposure: Challenges and Opportunities* NICHD
Award: $5,000
Contact: Rosemary Higgins

The workshop was held on March 23-24, 2004 to review the data collected to date on the maternal lifestyle study conducted over the last decade at four universities. Following presentations and discussions, the participants discussed the environmental and other determinants (maternal depression, sexual and physical abuse, and education) underlying associations between prenatal exposure and developmental outcomes.

▶ Title: *Advancing Diagnostic Approaches for Temporomandibular Joint Diseases and Disorders* *NIDCR*
Award: $5,000
Contact: John Kusiak

The meeting, held in May 2004, focused on applications of new technology to diagnose temporomandibular disorders; many advances come from studies related to other forms of musculoskeletal injuries and disease. The educational objective included: the current approaches used for the diagnosis of TMJ diseases and disorders; how new and emerging diagnostic technologies can be applied to the TM joint; understanding the complexity of TMJ diseases and disorders; understanding the limitations in predicting outcomes of specific treatments for individuals; and becoming aware of the NIH recommendations for conservative treatments, with irreversible treatment selected as a last resort.

▶ Title: *International Conference on Women and Infectious Disease* CDC
Award: $10,000
Contact: Marian McDonald, Dr. P.H.

The National Center for Infectious Diseases, the Centers for Disease Control and Prevention, and numerous partners held a conference in February 2004. The goal of the conference was to enhance prevention and control of infectious disease among women worldwide. The conference consisted of several plenary sessions and breakout sessions featuring numerous topics addressing, for example, the impact of globalization, women and HIV, perinatal infectious diseases, immunizations, antimicrobial resistance, and linkages between infectious and chronic diseases.

▶ Title: *Computer-based Technology and Care Giving of Older Adults* NIA
Award: $5,000
Contact: Dr. Sydney Stahl

The conference was held in the Natcher Center at the National Institutes of Health in October 2003. The purpose of this conference was to elevate awareness in the family care giving community throughout the United States to the rapidly increasing importance of computer-based technology in helping support quality care giving for older Americans.

▶ Title: *American Society for Cell Biology*
Award: $5,267
Contact: Elizabeth Marincola

The ORWH provided funds for the 44th American Society for Cell Biology Annual Meeting to be held in Washington, DC, in December 2004. Funds will be designated to the support of the AXXS Special Interest Subgroup, Advancing the Careers of Women Scientists: A Role for Everyone.

APPENDIX I

Intramural Programs on Research on Women's Health Steering Committee, 2004

Co-Chair
Dr. Esther Sternberg, NIMH
Dr. Barbara Vonderhaar, NCI

Dr. Joan Schwartz, OD, OIR
Dr. Janine Smith, NEI, WHSIG Coordinator
Dr. Vivian Pinn, Director, ORWH, OD
Dr. Marc Blackman, NCCAM
Dr. Giovanni Cizza, NIMH
Dr. Elizabeth Fee, NLM
Dr. Jennifer Eng-Wong
Dr. Lynn Gerber, CC
Dr. Michael Gottesman, OD, OIR
Dr. Hynda Kleinman, NIDCR
Dr. Kenneth Korach, NIEHS
Dr. James Lacey, NCI
Dr. Lawrence Nelson, NICHD
Dr. Monica Skarulis, NIDDK
Dr. Jeffrey Struewing, NICHD
Dr. Susan Wray, NINDS
Dr. Richard Wyatt, OD, OIR
Ms. Joyce Rudick, OD, ORWH
Ms. Vicki Malick, OD, OIR/ORWH

Former Member
Dr. Jo Anne Zujewski, NCI

APPENDIX J
Women's Health Special Interest Group Lectures, FY 2003 and 2004

October 21, 2002

The Impact of Sex and Gender on Human Physiology and the Experience of Disease

Marianne J. Legato, M.D.
Columbia University
College of Physicians and Surgeons

November 8, 2002

Estrogen Receptors—From Molecular Biology to Therapeutics

Jan-Ake Gustafsson, M.D., Ph.D.
Karolinska Institute, Sweden

December 20, 2002

Prolactin in Breast Development and Cancer

Barbara K. Vonderhaar, Ph.D.
National Cancer Institute

January 29, 2003

Depression: A Risk Factor for Osteoporosis in Women:
Lessons from the P.O.W.E.R. Study as a Model for Integrative Clinical Research at NIH

Giovanni Cizza, M.D., Ph.D.
National Institute of Mental Health

Depression and the Perimenopause

Peter Schmidt, M.D.
National Institute of Mental Health

March 26, 2003

The Prevention of Breast Cancer
Effects of Raloxifene in Pre-menopausal Women
Future Directions for Research

Jo Anne Zujewski, M.D.
National Cancer Institute

April 25, 2003

Estrogen-dependent and -independent Regulation of Immune System Development

Paul Kincade, Ph.D.
Oklahoma University

May 21, 2003

Sex Hormone Effects on Specific Brain Mechanisms and on Generalized Brain Arousal

Don Pfaff, Ph.D.
Rockefeller University

June 11, 2003

Autoimmune Disease—Why Female?

Nancy Olsen, M.D.
Vanderbilt University

October 29, 2003

Estrogen and Synapses in the Hippocampus

Catherine Woolley, Ph.D.
Northwestern University

December 10, 2003

Molecular-targeted Theapeutics and Proteomics in Ovarian Cancer

Elise Kohn, M.D.
National Cancer Institute

January 9, 2004

Autoimmune Diseases in Women

Denise L. Faustman, M.D.
Harvard Medical School/MGH

February 6, 2004

Evaluating Differential Estrogen Receptor Activities Using Knockout Mouse Models

Kenneth Korach, Ph.D.
National Institute of Environmental Health Sciences

April 16, 2004

Estrogen Actions in Cardiovascular Physiology: 2004 Update

Michael E. Mendelsohn, M.D.
New England Medical Center/Tufts University

September 17, 2004

Identifying the Body Mass Index of Risk for African Americans

Anne E. Sumner, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

December 17, 2004

Exercise and Women's Health: Basic and Clinical Applications

Patricia A. Deuster, Ph.D., M.P.H.
United States University of the Health Sciences

APPENDIX K

Office of Research on Women's Health Women's Health Seminar Series

Respiratory Health and Diseases in Women
January 14, 2003

Lung Diseases in Women: Overview
Christopher Fanta, M.D.
Brigham and Women's Hospital

Asthma Epidemiology
Carlos A. Camargo, M.D., Dr.P.H.
Massachusetts General Hospital

Management of Respiratory Disease by Patients
Noreen M. Clark, Ph.D.
University of Michigan School of Public Health

Smoking Cessation: Targeting Women
Cynthia S. Rand, Ph.D.
Johns Hopkins School of Medicine

Cancers in Women: New Approaches
May 29, 2003

Energy Balance and Cancer in Women: Evidence, Gaps, and Challenges
Rachel Ballard-Barbash, M.D., M.P.H.
National Cancer Institute

Ductal Carcinoma in situ*: Morphology and Biology*
James I. Connolly, M.D.
Beth Israel Deaconess Medical Center

Ovarian Cancer Detection and Treatment Monitoring
Elise C. Kohn, M.D.
National Cancer Institute

Preventing Cervical Cancer by Human Papillomavirus Vaccines
Douglas Lowy, M.D.
National Cancer Institute

Alcohol: A Women's Health Issue
October 23, 2003

Alcohol and Women: The Big Picture
Mary C. Dufour, M.D., M.P.H. (retired)
National Institute on Alcohol Abuse and Alcoholism

Treatment Issues and Outcomes for Alcohol-dependent Women
Karen Clay Rhines, Ph.D.
Seton Hall University

Alcohol and Intimate Partner Violence
Kenneth E. Leonard, Ph.D.
State University of New York at Buffalo

Boning Up On Osteoporosis: Emerging Therapies for Prevention and Treatment
December 9, 2003

Introductory Remarks
Joan A. McGowan, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Role of Nutrition in Building Peak Bone Mass
Connie M. Weaver, Ph.D.
Purdue University

Seeing a Silent Disease: Skeletal Imagine in Osteoporosis
Mary L. Bouxsein, Ph.D.
Beth Israel Deaconess Medical Center

Evolution in Clinical Strategies: Putting It All Together
Deborah E. Sellmeyer, M.D.
University of California–San Francisco

Panel Discussion/Questions and Answers
Chaired by Allan S. Noonan, M.D., M.P.H.
Office of the Surgeon General

Invited Panels
Joan R. Goldberg, Executive Director
American Society for Bone and Mineral Research

Women and Heart Disease
March 18, 2004

Women and Heart Disease: What You Don't Know CAN Hurt You!
An Overview
Sharonne N. Hayes, M.D., FACC, Cardiologist
Director, Mayo Clinic Women's Heart Clinic
Associate Professor of Medicine
Mayo Graduate School of Medicine

Hormone Replacement: The Heart Facts
Pamela Ouyang, M.D., Cardiologist
Associate Professor of Medicine
Johns Hopkins University, School of Medicine

Fit for Life: Avoiding Obesity and Heart Disease Through Nutrition and Exercise
Njeri Karanja, Ph.D., Senior Investigator
Kaiser Permanente Center for Health Research

Getting Women to See Red: The Heart Truth Campaign
Ann M. Taubenheim, Ph.D., M.S.N.
Coordinator, Women's Heart Health Education Initiative
National Heart, Lung, and Blood Institute

Questions and Answers

Alternative Medicine and Women's Health
June 3, 2004

Overview of Complementary and Alternative Medicine
Margaret A. Chesney, Ph.D., Deputy Director
National Center for Complementary and Alternative Medicine
National Institutes of Health

Integrative Medicine Approaches to Fibromyalgia and Osteoarthritis
Janine Blackman, M.D., Ph.D., Assistant Professor and Medical Director
University of Maryland Integrative Medical Center

Botanicals That Affect Women's Health
Norman Farnsworth, Ph.D., Director
Program for Collaborative Research in the Pharmaceutical Sciences
University of Illinois

Meditation, Yoga, and Tai Chi For Health and Well Being
Majorie Woollacott, Ph.D., Professor
Institute of Neuroscience
University of Oregon

Question and Answer Session

Acronyms

ACRONYMS USED IN THIS REPORT

ACRWH	Advisory Committee on Research on Women's Health
CC	Clinical Center
CCRWH	Coordinating Committee on Research on Women's Health
CDC	Centers for Disease Control and Prevention
DCRT	Division of Computer Research and Technology
DHHS	Department of Health and Human Services
DRG	Division of Research Grants
FDA	Food and Drug Administration
FIC	Fogarty International Center
GAO	U.S. General Accounting Office
HRSA	Health Resources and Services Administration
IC	Institutes and Centers of the National Institutes of Health
IOM	Institute of Medicine
NCHGR	National Center for Human Genome Research
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIJ	National Institute of Justice
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OAM	Office of Alternative Medicine
OAR	Office of AIDS Research, Office of the Director, NIH
OASH	Office of the Assistant Secretary for Health
OBSSR	Office of Behavioral and Social Sciences Research
OD	Office of the Director, NIH

OE	Office of Education, NIH
OEO	Office of Equal Opportunity, NIH
OER	Office of Extramural Research, Office of the Director, NIH
OIT	Office of Information Technology
ORDR	Office of Rare Disease Research
ORMH	Office of Research on Minority Health, Office of the Director, NIH
WHI	Women's Health Initiative
WSA	Women Science Advisors

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U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health
http://orwh.od.nih.gov
http://orwh.od.nih.gov/pubs/complete_ICD_report03_04.pdf

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