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 2005 & 2006

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 2005 & 2006

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Preface

The Advisory Committee on Research on Women's Health (ACRWH), 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, Centers, and Offices to address women's health issues through research and related activities supported in fiscal years (FY) 2005 and 2006. 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:

- 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 an interdisciplinary 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] 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, Centers (ICs), and Offices contained herein and believes that this report accurately reflects the breadth and depth of research and related activities through which the NIH fulfilled its mandate from the U.S. Congress to address women's health issues and women's inclusion in research in FY 2005 and 2006. 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 CCRWH, the NIH Office of Financial Management (OFM), the NIH ORWH, and the United States (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 interdisciplinary research on women's health in concert with the NIH ICs and Offices, 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 FY 2005 and 2006. 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, universities, medical schools, and research institutions nationwide.

The executive summary features program highlights from the NIH ICs and Offices, as well as analyses of funding of research on specific diseases and conditions presented in tabular format. Full reports submitted by ICs and Offices constitute the greater part of this report. Research supported by the ORWH during FY 2005 and 2006 is presented in the appendices.

The ACRWH acknowledges the valuable contributions of the NIH CCRWH, which is made up of the directors of each of the ICs and Offices (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 OFM in collecting and tabulating the budgetary data published in this report.

Finally, the ACRWH acknowledges the work of the ORWH staff. This report reflects the achievements of the 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, 2007

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Contents

Appendices

Introduction

When the National Institutes of Health announced that it was establishing an Office of Research on Women's Health (ORWH) in September 1990, there were great expectations of what might result, but it is unlikely that, at that time, anyone expected the magnitude of programs and accomplishments related to women's health research and careers that would flourish across the NIH in the years that would follow.

The ORWH became the first office within the Department of Health and Human Services to have the specific purpose of addressing women's health issues, yet its initial intent was to abate the criticisms that NIH did not have a consistent or enforced policy that required the inclusion of women in the research that it funded, especially when that research was on conditions that were not female specific. Over the years that have followed, the NIH Institutes and Centers, often with ORWH's collaborative support, have funded research that addresses specific gaps in knowledge about women. But they also have independently given increasing attention to ensuring research that allows comparisons of differences, or similarities, between men and women in responses to interventions being examined through clinical research. And, these concepts are beginning to penetrate the thinking at the basic laboratory research level, although without a specific NIH policy requirement. While the ORWH has specific goals to enhance women's health research, develop programs to promote biomedical career advancement for women, and, for both men and women, to conduct women's health research or studies that provide sex/gender aspects of health by comparing men and women in their responses to the interventions studied, the ORWH has continued its initial mission by leading trans-NIH efforts for consistent monitoring of the inclusion of women and minorities in clinical research.

This report is a comprehensive summary of all of the activities and programs of the ORWH, as well as an Executive Summary followed by more detailed information of highlights of women's health research within the NIH ICs and Office of the Director Program Offices.

Many continue to attempt to evaluate progress on women's health research by referring to budgetary expenditures on women's health when compared to men's health. This is not the most reliable way to assess progress, primarily because basic laboratory studies are at the foundation of progress about women's health, and often such basic studies have the potential to increase knowledge about both men and women, or serve as the foundation for ensuing clinical research. Further, with the current concepts of women's health extending beyond that of the reproductive system, and with the NIH policy of inclusion requiring that both men and women be included in clinical research on conditions that affect them—therefore, referring to research that is not female specific, both sexes are included in the studies. The result is that NIH research dollars must be summarized as that related to women's health research, that related to men's health research, and that related to, or including, both men and women. Consequently, the figures reported as specific for women's health research must be considered to be less than the total spent to explore women's health, with consideration of the additional amount listed under both. A section included in this report, based upon figures provided by the ICs, provides specific amounts for FY 2005 and FY 2006 included in this report.

Approximately $3.5 billion was spent each year on sex/gender-specific research related to women's health. In addition, over $22.5 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. Another way of reporting this data is that almost 13 percent of the NIH research budget was expended on research specific to women, almost 6 percent was expended on research specific to men, while the overwhelming majority (over 81 percent) of research funds were spent on research that either included both women and men, or was laboratory investigation that was important for exploring the health of both women and men.

In accordance with the NIH Revitalization Act of 1993[2], 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)[3] to provide these programmatic summaries of NIH research and other efforts related to women's health in FY 2005 and 2006. The ORWH also describes its role in catalyzing interdisciplinary career development and research centers on women's health and sex/gender research. In addition, the Office develops programs to strengthen and foster women's participation and advancement in biomedical careers and to promote careers for both men and women to conduct women's health or sex/gender based research. A complete listing of research, career development, and other projects supported by the ORWH during FY 2005 and 2006 is included in the appendices. The specific trans-NIH activities that monitor and track the inclusion of women and minorities in clinical research are also described. Highlights of women's health and sex/gender research supported by the NIH institutes, centers, and offices are also included in this report. 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. The Offices within the Office of the NIH Director have also contributed to this research and this report.

A major ORWH research area relates to interdisciplinary programs. One of these programs is the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR). Eleven SCOR Centers have demonstrated exciting new developments from 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 research bridging basic and clinical sciences on sex and gender factors underlying a priority health issue. Research areas addressed by the centers include mental health, reproductive health, pain disorders, substance abuse, and urinary tract health. The SCOR program complements other federally supported programs addressing women's health issues. Another major interdisciplinary program is the Building Interdisciplinary Research Careers in Women's Health (BIRCWH). The BIRCWH program grants provide an opportunity for institutions to be involved in women's health and sex/gender oriented research and to build a national supply of investigators by providing research training in conjunction with strong scientific and career mentoring that will enhance the career development of the women and men who are selected as scholars. This program has made impressive progress, with the 35 BIRCWH centers producing 287 scholars, most of whom have gone on to academic positions and received NIH grant awards. Other career development programs supported by the ORWH include the Women's Reproductive Health Research Career Development Centers (WRHR) of the National Institute of Child Health and Human Development, and numerous other NIH RFAs and PAs.

The NIH ICs and Offices present a brief accounting of their scientific advances in the Executive Summary section of this report. More detailed discussions of these advances are included in the section on Reports of the Institutes, Centers, and Offices.

This report is prepared for, and reviewed by, the Advisory Committee on Research on Women's Health, that has the responsibility for preparing a report on the activities related to women's health at the NIH.

You are invited to read this in-depth report to become acquainted with the tremendous advancements that have taken place during this 2-year period and the promise for even greater advancements in the future, representing the broad diversity and success of the ORWH, and the trans-NIH activities to advance the health of women and men, and career opportunities in biomedical sciences.

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

[2] Public Law 103-43, 107, stat, 22 (codified at 42 USC [sec.486 (A)].
[3] See pages 17-20 for a list of the CCRWH members.

ORWH Staff Roster, 2005

Vivian W. Pinn, M.D.	Associate Director for Research on Women's Health Director, ORWH
Julia Alquijay	Secretary
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Angela Bates, M.B.A.	Program Analyst
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Teresa Kendrix	Administrative Officer
Kimberly Kurilla-Gray	Secretary to the Director
Mary Lawrence, M.S.	Program Analyst
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Joyce Rudick	Director, Programs and Management
Juanita Savelli	Program Assistant
Charles A. Wells, Ph.D.	Program Analysis Officer (on detail from NIEHS)

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CSR	Denise Wiesch, Ph.D.	Scientific Review Administrator

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NIDCR	Maria Canto, D.D.S.	Director, Health Promotion and Community-Based Research Program
OAR	Vicki Cargill, M.D.	Director of Minority Research, Director of Clinical Studies
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NHGRI	M.K. Holohan, J.D.	Health Policy Analyst
OPLA	Anne Houser	Senior Legislative Analyst
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NIA	Kate Nagy, M.A.	Program Analyst
ODS	Mary Frances Picciano, Ph.D.	Senior Nutrition Research Scientist
NCCAM	Carol Pontzer, Ph.D.	Program Officer
NINDS	Linda Porter, Ph.D.	Program Director, Systems and Cognitive Neuroscience Cluster
NIMH	Catherine Roca, M.D.	Chief, Women's Programs
NICHD	Mona Rowe, M.C.P.	Associate Director for Science Policy Analysis and Communication
NCMHD	John Ruffin, Ph.D.	Director
NIAAA	Denise Russo, Ph.D.	HSA, Division of Metabolism and Health Effects
NIEHS	Anne Sassaman, Ph.D.	Director, Division of Extramural Research and Training
NIDCD	Lana Shekim, Ph.D.	Director, Voice and Speech Program
OIR	Esther Sternberg, M.D.	Chief, Section on Neuroendocrine Immunology and Behavior
NIAMS	Maddy Turkeltaub, Ph.D.	Deputy Director, Extramural Programs
NIDA	Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator
CSR	Denise Wiesch, Ph.D.	Scientific Review Administrator

NIH Coordinating Committee on Research on Women's Health Alternates, 2006

Institute, Center, or Office	*Alternate*	*Title*
NIAID	Diane Adger Johnson	Minority Health and Research Training Analyst
OCPL	Marin Allen, Ph.D.	Deputy Director
NINR	Paul Cotton, Ph.D.	Program Director, Division of Extramural Activiti
NIBIB	Anthony Demsey, Ph.D.	Director, Extramural Policy
NIDCD	Amy Donahue, Ph.D.	Chief, Hearing and Balance/Vestibular Sciences Branch
NIGMS	Paula Flicker, Ph.D.	Program Director
NHGRI	Phyllis Frosst, Ph.D.	Science Policy Analyst
NIDDK	Mary Hanlon, Ph.D.	Health Science Policy Analyst
FIC	Sharon Hrynkow, Ph.D.	Deputy Director
NIDA	Aurora Hutchinson	Deputy, Women and Gender Research Coordinator
CC	Walter Jones, M.S.	Deputy Director for Diversity Operations
NCMHD	Mireille Kanda, M.D.	Deputy Director
NIA	Karin Kolsky, B.A.	Writer/Editor
NEI	Natalie Kurinij, Ph.D.	Health Science Administrator
NCRR	Sheila McClure, Ph.D.	Health Scientist Administrator
OAR	Denise Miles	Program Analyst
OCL	Walter Mitten	Community Relations Specialist
NIEHS	Sheila Newton, Ph.D.	Director, Office of Policy, Planning, and Evaluation
NCI	Cherie Nichols, M.B.A.	Director, Office of Science Policy and Analysis
NIDCR	Ruth Nowjack Raymer	Program Director, Health Disparities Research
NIMH	Kathy O'Leary, M.S.W.	Deputy Chief of Women's Programs
NICHD	Estella Parrott, M.D.	Program Director, Reproductive Sciences Branch
OEODM	Rose Pruitt	Federal Women's Program Manager
NIAAA	Deidra Roach, M.D.	Health Science Administrator
NINDS	Daphne Robinson, Ph.D.	Office of Science Policy and Planning
NHLBI	Susan Scolnik	Program Analyst
CSR	Elaine Sierra Rivera, Ph.D.	Scientific Review Administrator
OSP	Lana Skirboll, Ph.D.	Director
OIR	Pat Sokolove, Ph.D.	Director, Interdisciplinary Training Program
NCCAM	Kate Stoney, Ph.D.	Program Officer
OIR	Barbara Vonderhaar, Ph.D.	Chief, Molecular and Cellular Endocrinology Section

Office of Research on Women's Health

ESTABLISHMENT OF ORWH

In 1983, the 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." 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.[4]

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."[5]

Following the issuance of the report of the Public Health Service (PHS) Task Force on Women's Health in 1985, the 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 that year, minority scientists and other researchers at NIH recognized the need to address the inclusion of minority populations. As a result, a later 1987 version of the NIH Guide published for the first time a policy encouraging the inclusion of minorities in clinical studies.

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 the NIH. This report, included in congressional testimony, indicated that the implementation of the policy for the inclusion of women was lacking, 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.[6] 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.

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

[4] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508 (1994)
[5] *Women's Health: NIH has Increased Its Efforts to Include Women in Research* (GAO/HEHS-00-96, May 2000)
[6] *National Institutes of Health: Problems in Implementing Policy on Women Study Populations* (GAO/T-HRD-90-38)

- 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

This report on women's health at the NIH for FY 2005 and 2006 marks the 16th anniversary of the ORWH. The ORWH was the first office in DHHS to address women's health. At its inception in September 1990, the primary mission of the Office was to respond to concerns related to a lack of systematic inclusion of women in NIH-supported clinical research trials. Since that time, the scope of interest and responsibility of the ORWH has expanded greatly. Research supported by the NIH has afforded much progress in understanding a range of issues related to women's health, including sex and gender factors that affect a number of diseases and health conditions. The NIH approach to both clinical and basic research now encompasses the entire life span of women. Progress to date is evidenced by research findings related to women and minorities as well as the establishment of research priorities to fill existing gaps in knowledge and to address emerging scientific questions. This expansion of effort and knowledge is not simply the result of ORWH activities; it also reflects the efforts of the NIH ICs as well as other programs within the OD at the NIH.

One element of the mission of the ORWH is to stimulate and encourage meritorious research on women's health, including the role of sex and gender in health and disease. Women's health research and the study of sex and gender factors continued to expand both in complexity and scope in FY 2005 and 2006. Although ORWH does not have grant-making authority as do the NIH ICs, the ORWH does serve as the catalyst and coordinator for activities in the area of women's health research across the NIH. All NIH IC and OD program offices with research portfolios support or co-fund biomedical and behavioral research projects related to women's health. These projects are highlighted in this report. The ORWH also collaborates with other agencies in DHHS and with the broader scientific, health professional, and advocacy communities to determine areas for which further research on women's health is needed and to implement the recommendations from the report, *Agenda for Research on Women's Health for the 21st Century*. Moreover, the ORWH takes a multimedia approach to communicate the advances being made from past and current research, maintains a Web site, produces a monthly podcast on women's health, provides education through distribution of informational documents and videotapes of conferences, provides an online sex and gender course, and reaches out to the general public, advocacy groups, health professionals, and organizations to generate interest in women's health.

To keep the research agenda current, an *ad hoc* Research Subcommittee of the CCRWH (see Appendix A for detailed list of members) annually reviews the current research and identifies critical scientific opportunities and research priorities that address gaps in knowledge and emerging scientific issues in women's health. This group recommends to the ORWH those scientific areas that are determined to be of special importance for expanding current initiatives or for developing new research programs. The recommended research priorities are reviewed and discussed for their appropriateness for NIH research by the full CCRWH. The ACRWH, in a final review, modifies or approves the recommended research priorities to the ORWH.

The list of research priorities is by no means comprehensive nor does it intend to limit new studies to only those topics. Rather, the recommended priorities signify areas which the NIH wishes to stimulate and encourage research on women's health or sex and gender factors affecting health. The priorities may also address the need to expand current or past research that did not adequately address sex and gender analysis or provide a specific focus on women. Moreover, priorities identify areas and approaches for the advancement of women in biomedical research careers.

The following section of the biennial report describes the activities of the ORWH. The reports from the NIH ICs and Offices follow. The ORWH section is organized around the major missions of the Office, namely research, monitoring the inclusion of women and minorities in clinical research, biomedical careers, conferences and workshops, and outreach. It starts with the NIH Research Priorities for Women's Health for both FY 2005 and 2006, which address overarching themes calling for research in women's health, enumerates areas of research interest, and describes special emphasis areas. Several themes are addressed in both fiscal years, highlighting the importance and complexities of these issues, noting progress made, and underscoring the cumulative process of building a sound scientific foundation for women's health. Information on specific research projects funded or co-funded by the ORWH in FY 2005 and 2006 follows. Individual projects are grouped by diseases and conditions affecting women's health. As research has produced important data on women's health, the research questions have become more complex, often requiring the contributions of scientists from different disciplines. Thus, the description of research includes information on interdisciplinary programs supported by the ORWH that encompasses critical research projects, as well as career development in women's health and sex/gender research. Because the purview of the ORWH spans the diseases and conditions of women covered by the various NIH ICs and Offices, it is uniquely positioned to serve as the coordinator for research across the NIH. For example, the Office coordinates the trans-NIH research efforts for chronic fatigue syndrome (CFS). Thus, the research component of this report includes a description of the CFS program and associated research portfolio. After the research section, the report covers monitoring inclusion of women and minorities in clinical research, biomedical careers, conferences and research planning workshops, and outreach. However, the mandate of the ORWH goes beyond research to include career development. To ensure future progress of research on women's health, it is important to train scientists to work in this area. Thus, this report includes a section on programs to develop biomedical careers for research on women's health and sex/gender factors.

In addition to programs for biomedical careers, the ORWH has developed Web-based instruction in the importance of sex and gender factors in health to inform those already engaged in health research and practice. In collaboration with the Food and Drug Administration (FDA) Office of Women's Health (OWH), ORWH launched the course, *The Science of Sex and Gender in Human Health*, in June 2006. The course offers participants a basic scientific understanding of the major physiological differences between the sexes, their influence on illness and health outcomes, and their implications for policy, medical research, and health care. Designed for researchers, clinicians, members of academia, and students in health professional schools, the course built on the Institute of Medicine (IOM) report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* This report was issued in 2001 and received support from the HHS, OWH, NIH ORWH, FDA, and the Society for Women's Health Research along with other federal and private agencies. The course, which is free to the public, is self-administered. It comprises six lessons that cover the definitions of sex and gender, the development and implementation of federal research regulations, cell physiology, developmental biology, pharmacodynamics and pharmacokinetics, and clinical applications of genomics. The course is available online at http://orwh.od.nih.gov/. This activity was approved for six AMA PRA Category 1™ credits. Participants who complete the course receive a certificate from the NIH. Since its launching in 2006, 1,712 people have registered for the course. Based on information on their Internet service providers, 273 registrants come from government, 350 from educational institutions, 122 from other organizations, and the remainder from unspecified organizations. A second course module is currently in development. It will apply the basic concepts presented in the initial course to specific conditions where sex differences play a significant role.

The ORWH provides support for conferences and workshops on scientific topics related to its purview. The ORWH strives to

ensure that the information generated from the NIH investment in research on women's health is informing future research efforts and the clinical care of women. It is important to note that the ORWH considers outreach to the larger population of clinicians, women, and other interested people to be a very important part of its mandate. Thus, the Office provides information on a range of outreach activities as follows.

Research

The ORWH seeks to strengthen and enhance research related to diseases, disorders, and conditions that may be unique for girls and women, as well as those that affect both men and women, but for which sex and gender differences may occur or have been documented. It also seeks to ensure that the broad array of research funded by the NIH adequately addresses women's health, and to ensure the inclusion of women and minorities in biomedical and biobehavioral research. The Office works in partnership with the NIH ICs and the extramural scientific communities to integrate women's health into the scientific framework of NIH and to establish research priorities for each year. As stated previously, the report begins with a description of the research priorities and programs for FY 2005 and 2006.

FY 2005 NIH Research Priorities for Women's Health

Overarching Themes

Four overarching themes are important for addressing any aspect of research on women's health. They include:

- Life Span,
- Sex/Gender Determinants,
- Health Disparities/Differences and Diversity, and
- Interdisciplinary Research.

Life Span

The health of girls and women is affected by developmental, physiological, and psychological age. Women's lives are marked by a continuum, from intrauterine life to the elderly years. Critical periods include infancy, childhood and adolescence, menarche, reproductive life, the menopausal transition, postmenopausal years, the elderly, and the frail elderly. Many women's lives and health status are influenced by other factors, such as work inside and outside the home, child care and elder care responsibilities, reproductive status, and chronic illness. Each of these factors 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 IOM report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* In this context, 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 among 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 several factors, such as culture, education, access to care, quality of care, and access to opportunities for inclusion as research subjects in clinical trials and studies. Thus, clinical research should include, but not be limited to, population-specific characteristics, such as cultural diversity, race/ethnicity, immigrant status, rural or inner city residency

status, poverty or low socioeconomic status and associated effects, sexual orientation, and physical or mental disabilities. Furthermore, basic research is needed to define biological factors that may underlie health disparities and population differences.

Interdisciplinary Research

With increased understanding of the interrelatedness and complexity of diseases, scientific investigation can benefit from collaborative, interactive approaches associated with interdisciplinary research. Advances in women's health can be better achieved by promoting partnerships across disciplines for basic, clinical, and translational research. A synergy of progress in research can result from interdisciplinary collaborations among researchers participating in federal programs that provide access to the latest scientific tools, technologies, and concepts for women's health research. These collaborations can involve researchers working in academia, private industry, and other federal settings. A number of interdisciplinary approaches are relevant to research on women's health, including bioengineering and biomedical informatics, genomics, proteomics, imaging, and metabolomics, and can facilitate research that integrates basic, clinical, and translational research, population studies, molecular and cellular investigations, behavioral and social science research, and health services and outcomes research.

Areas of Research Interest

Within the research continuum that spans basic, clinical, and translational studies, important questions remain concerning sex and gender differences. Research is needed to identify the optimal methods to translate knowledge gained from basic science research into clinical research and practice to improve clinical outcomes in women. Studies are needed to determine the best clinical practices to provide appropriate care for women and men. Information from this research not only increases the base of scientific and clinical knowledge, but it also is necessary for women and their clinicians to manage their health care decisions.

Through interdisciplinary collaborations, research can contribute to the development and evaluation of effective strategies to improve the quality of care and the quality of life for women. Better mechanisms to translate clinical research results into standards of health care and health policy are needed to improve women's health. In addition, providing feedback from clinical settings to scientists working at the bench can lead to new research hypotheses and projects.

The following list is illustrative of important research areas, but it is not exhaustive. Thus, areas of research interest include, but are not limited to:

- *In vitro* studies of chromosomal, genetic, gonadal, and phenotypic factors that are important in diseases affecting women, as well as similar *in vivo* studies in animal models;
- Etiologic mechanisms to elucidate sex differences in cells, tissues, or organs, with consideration to physiological and/or immune responses to environmental and infectious agents;
- Cellular and molecular studies of the mechanism of action and effects 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 behavior or the endocrine, musculoskeletal, autoimmune, urologic, cardiovascular, ophthalmic, and neurobiological systems;
- Systemic and cellular modeling of biological pathways and systems related to women's health;
- Clinical trial methodology related to studies of women, including ethical issues, study design, novel recruitment strategies, and novel statistical analysis techniques;
- Mental health studies, such as studies on the incidence, severity, and treatment of depression and other addictive, mood, cognitive, and anxiety disorders, including physical and physiological stressors;
- Studies on the effects of caregiving on the health of the caregiver and the effects of the multiple and competing societal roles of women on their health;

- Studies of behavioral correlates that affect the selection and advancement of women's careers in biomedical sciences;
- Studies of agents for optimizing the management of menopausal symptoms;
- Studies on the role of the menstrual cycle on the initiation and course of disease and the response to treatment;
- Studies on the effect of pregnancy and the postpartum period on disease;
- Research on the prevalence of sex differences in the diagnosis and treatment of diseases and disorders differentially affecting men and women as well as methods to validate these differences;
- Development of treatments and 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; and
- Collaboration on trans-NIH research initiatives, such as CFS and uterine fibroids.

Special Emphasis Areas

In FY 2005, the ORWH was especially interested in fostering research in women's health in two high-priority areas. These areas are *prevention and treatment*, and *the interaction of sex and genetics and pharmacogenomics*.

Prevention and Treatment

Increased investigation into methods to prevent or better treat conditions and diseases can result in significant improvements in the quality and length of women's lives. Prevention research spans the research continuum, from the most basic biological studies to clinical studies to understand and intervene on risk behaviors across the life span. Examples of prevention and treatment research needed in women's health include, but are not limited to the following areas:

- Research to identify and validate biomarkers of disease pathogenesis and risk and their application to disease prevention, early detection and treatment, including the development of novel tools;
- Studies of the health impact of diet, nutrition, hormones, exercise, weight patterns (including obesity and eating disorders), tobacco, alcohol and drug abuse, and violence;
- Research on reproduction, from menarche to pregnancy and the menopausal transition, as well as the effect of reproductive status on the susceptibility to and protection from specific diseases and conditions;
- Studies of the factors involved in disease initiation and progression with the goal of developing effective preventive and curative strategies;
- Research to develop, test, and validate 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 multisystem diseases; and
- Studies on the effect of biological, behavioral, cultural, social, economic, and environmental factors on the susceptibility to or protection from specific diseases and responses to treatment.

Sex and Genetics and Pharmacogenomics

Although there has been much activity in the last few years in the identification of the function of genes and their effect on treatment, more research is needed on the effects of sex as a modifier of gene function and response. The sequencing of the human genome allowed researchers to define the role of genetic polymorphisms and pharmacogenomics on disease development, course of illness, and response to current treatments. However, the role of confounding factors, including sex, on the function of genes and genetic polymorphisms in disease and treatment response has been largely ignored. More research is needed in this emerging area, particularly for those diseases that disproportionately affect women. Examples of research issues related to this special wemphasis area include, but are not limited to:

- Determination of sex differences that may modify the role of known gene defects or polymorphisms in diseases;

- Determination of the effect of phases of the menstrual cycle, hormones, pregnancy, and menopause on genetic penetrance of disease;
- Mechanism of sex effects on gene expression;
- Genetic, molecular, and cellular basis of action of pharmacologic agents known to have differential effects in women and men;
- Interaction of environmental exposures and genetic polymorphisms in diseases common to women;
- Role for genes known to be differentially expressed in women in the incidence, course, and response to treatment of common diseases;
- Impact of sex on genetic differences underlying pharmacokinetics, pharmacodynamics, drug efficacy, and adverse effects of drugs;
- Development of novel methods of analysis to discern interactions of sex and genes in mechanisms of disease initiation, course, and response to treatment;
- Role of age, sex, and gene interactions in diseases affecting women;
- Genetic polymorphisms that modify action of diet, drugs, or toxins during pregnancy on the mother and child; and
- Differences in gene expression that occur during the prenatal period, puberty, pregnancy, and beyond.

FY 2006 NIH Research Priorities for Women's Health

Overarching Themes

The same overarching themes enumerated in FY 2005 continue to be important for addressing research on women's health. They include:

- Life Span,
- Sex/Gender Determinants,
- Health Disparities/Differences and Diversity, and
- Interdisciplinary Research.

LIFE SPAN

The health of girls and women is affected by developmental, physiological, and psychological age. 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 the frail elderly. Reproductive health is an important area for women's health, which is reflected in research to improve the well-being of women and their offspring. The 2006 IOM report, *Preterm Birth: Causes, Consequences, and Prevention*, which received support from the ORWH as well as other federal and private organizations, made important recommendations for research and health care for pregnant women. However, women's health is influenced by factors much broader than reproductive issues. Many women's lives and health status are influenced by other factors, such as work inside and outside the home, child care and elder care responsibilities, reproductive status, marital 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 IOM report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* In this context, 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 among 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 several factors, such as biology, genes, culture, education, access to care, quality of care, and access to opportunities for inclusion as research subjects in clinical trials and studies. Thus, clinical research should include, but not be limited to, population-specific characteristics, such as cultural diversity, race/ethnicity, immigrant status, rural or inner-city residency status, poverty or low socioeconomic status and related effects, sexual orientation, and physical or mental disabilities. Further basic research studies are also needed to help define biological and other factors that may underlie health disparities and population differences.

Interdisciplinary Research

With increasing understanding of the interrelatedness and complexity of disease, the nature of scientific investigation can benefit from an interdisciplinary collaborative approach. Advances in women's health can be better achieved by promoting partnerships across disciplines for basic, clinical, and translational research. Interdisciplinary approaches can integrate knowledge from multiple specialties, thus defining underlying common pathologic processes. A synergy of progress in research can result from interdisciplinary collaborations among researchers working in academia, private industry, and federal settings to provide access to the latest scientific tools, technologies, and concepts for women's health research.

Areas of Research Interest

Areas of research interest cover a broad range of topics with some requiring an interdisciplinary perspective. The goal of highlighting these areas is to stimulate and encourage research in areas for which there are limited existing data to answer critical questions related to women's health or barriers to women seeking careers in research on women's health. Targeted research efforts include population studies, molecular and cellular investigations, behavioral and social sciences research, and health services and outcomes research. Examples of research addressing priority areas in women's health research include, but are not limited to, the following areas.

Diseases and Conditions that Affect Women

Studies are needed to investigate the pathogenesis and to develop preventive and therapeutic interventions for acute and chronic diseases and disorders that affect women, including, but not limited to, metabolic, inflammatory, endocrine, autoimmune, gastrointestinal, liver, urologic, ophthalmic, oral, reproductive, musculoskeletal, neurological, psychiatric, and cardiovascular diseases.

Methodological Advances

Research is needed to develop clinical trial methodologies, including novel recruitment strategies and statistical analysis methodologies that address ethical and study design issues specific to studies of women. Studies are also needed to develop new methodologies for animal model studies of diseases and normal development of women, including use of female animals. Methodological studies are needed as they relate to the conceptualization, distinction, and detection of sex and gender differences in basic and clinical biomedical research.

Education and Career Development of Women in Science

Research is needed to identify and explore factors that affect the selection and advancement of women's careers in biomedical sciences, to implement novel education programs directed at girls and women, and to promote unique programs for addressing impediments to the advancement and effective mentoring of women to senior positions in science.

Quality of Life

Research is needed to elucidate the unique sex and gender factors affecting women's quality of life and to develop approaches to the management of disease and the promotion of wellness that are directed at women and their unique issues.

Trans-NIH Collaboration

Women's health issues cut across the focus areas of the NIH ICs and, as such, these issues benefit from trans-NIH research partnerships and collaborations. Such partnerships and collaborations need to be fostered and encouraged, not only in all areas of research that affect women and women's health, but also in women's career development. The resultant research from these trans-NIH partnerships and collaborations will contribute to better standards of health care and health policies.

Special Emphasis Areas

The NIH is especially interested in fostering research in women's health in the high-priority areas of prevention and treatment. It is also interested in fostering research on the biological and behavioral basis of sex and gender differences.

Prevention and Treatment

Increased investigation into methods to prevent or better treat conditions and diseases can result in significant improvements in the quality and length of women's lives. Prevention research spans the research continuum from the most basic biological studies to clinical research to understand and intervene on risk behaviors across the life span. Research findings can inform interventions to change the behaviors, including risk-associated, wellness, and healthy behaviors. Examples of needed prevention and treatment research studies in women's health include, but are not limited to, the following areas:

- Research to identify and validate biomarkers, including genetic polymorphisms, of disease risk, pathogenesis, progression, and their applications to disease prevention, early detection, and treatment, including the development of novel tools;
- Studies of the impact on health of diet, nutrition, hormones, exercise, weight patterns, toxin exposures, obesity, eating disorders, sex practices, tobacco, alcohol and drug use or abuse, occupation, violence, or trauma;
- Studies of the factors that are involved in disease initiation and progression, both biological and behavioral, to develop effective preventive and treatment strategies;
- Development, testing, and validation of preventive, early detection, and treatment strategies for conditions and diseases, including, but not limited to, sexually transmitted diseases, cancer, coronary artery disease, stroke, obesity, diabetes, musculoskeletal disorders, pain syndromes, addictions, and chronic multisystemic diseases; and
- Studies of the effect of biological, behavioral, cultural, social, economic, and environmental factors on susceptibility to or protection from disease and response to treatment.

Biological and Behavioral Basis of Sex and Gender Differences

Although there has been much research to identify the function of cellular pathways and genes, research on the effects of sex as a modifier of cellular and gene function is underinvestigated. Systemic and cellular modeling of the influence of sex differences in biological pathways and systems is needed. Other research needed includes, but is not limited to, the following areas:

- Research to determine sex differences that may modify the role of known cellular pathways and gene defects in disease;
- Studies on sex and gender differences in prevention, pathogenesis, disease course, response to treatment, and prevention, using basic, translational, behavioral, and clinical research approaches;
- Research on mechanism of sex effects on gene expression and cellular and signaling pathways in healthy women, including the impact of puberty, the menstrual cycle, pregnancy, and menopause;
- Studies on the genetic, molecular, and cellular basis of action of pharmacologic agents in women, including differential effects between males and females;
- Studies to develop novel methods of analysis to assist in discerning impact of sex in mechanisms of disease initiation, disease course, and response to treatment or interventions; and

- Research on the effect of biologic and behavioral sex and gender difference on quality of life and quality of care.

Research Projects Funded or Co-Funded by ORWH in FY 2005 and 2006

The ORWH partners with the NIH ICs to fund or co-fund meritorious projects that advance the mission and scientific priorities of the NIH and add to the growing body of evidence about women's health and sex/gender factors. The annual report on *NIH Research Priorities for Women's Health* (see previous section) serves as a guide for the ORWH in selecting meritorious grants and contracts to support with the ICs. It also reflects emerging areas of interest or importance to women's health research. However, research supported by the ORWH is not limited to the enumerated priorities.

The tables below list the research grants and contracts that the ORWH supported with the NIH ICs for FY 2005 and FY 2006. Research summaries for FY 2005 and 2006 are found in Appendices B and C, respectively. In both FY 2005 and 2006, the ORWH collaborated with 17 NIH ICs as well as the DHHS Agency for Healthcare Research and Quality (AHRQ) and the Indian Health Service. In doing so, the Office funded or co-funded more than 100 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 the ORWH in the areas of aging; alcohol and other substance abuse; cancer; cardiovascular disease; CFS; craniofacial disorders, such as temporomandibular joint and muscle disorders (TMJD); diabetes; endricrinology; gastroenterology; genitourinary; HIV/AIDS; immunity/autoimmunity; infectious diseases; menopause; mental health; microbicides; musculoskeletal disorders and diseases; nutrition; obesity/overweight; ophthalmic disorders; pain; physical activity; reproductive health and developmental biology, including menopause-related topics and uterine fibroids; and violence.

The research funded by the ORWH addressed the full spectrum of a woman's life span, from the prenatal period to advanced age and frailty. Attention to sex/gender factors and health disparities was a recurring issue throughout the total research grant portfolio funded by ORWH. Tables 1 and 2 highlight the research projects funded or co-funded by the ORWH during FY 2005 and 2006. Research titles are grouped by broad topical subject areas, such as aging, cancer, and cardiovascular disease.

TABLE 1
ORWH Co-Sponsored Research Initiatives, FY 2005

Subject	*Title**	*IC†*	*Award Amount*
Aging	Phytoestrogens and Aging: Dose, Time and Tissue	NIA	$ 100,000
Alcohol and Other Substance Abuse	Sex Differences in Opioid Analgesia	NIDA	50,000
	Reducing Alcohol and Risks among Young Females	NIAAA	150,000
	Substance Use and Girls: Stress, Hormones, and Puberty	NIDA	171,563
	Impulsivity Related to Cocaine Dependence and Trauma	NIDA	87,440
	Tobacco Cessation Treatment for Pregnant Alaska Natives	NIDA	146,700
	Gender Responsive Treatment for Women in Prison	NIDA	139,940
Cancer	Clinical Trials of Two HPV-like Particle Vaccines	NCI	600,000
	Tumorigenic Subversion of Mural Cells in Breast Cancer	NCI	129,000
	Pharmacogenetics of the Endocrine Treatment of Breast Cancer	NIGMS	250,000
	Patient-centered Communication during Chemotherapy	NCI	50,000
Cardiovascular Disease	Genetics of Early-Onset Stroke	NINDS	300,000
	Sex Differences in Purkinje Cell Sensitivity to Ischemia	NINDS	200,000
	Altered Glucose and Lipid Metabolism in Obesity and CVD	NHLBI	200,000
	Inflammation and Insulin Resistance in Peripheral Arteria Disease	NHLBI	10,000
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	36,544
Chronic Fatigue Syndrome	Prospective Study of CFS in Adolescents	NICHD	300,000
	Risk Factors Associated with CFS	NIAID	100,000
Craniofacial Disorders	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 TMJ	NIDCR	100,000
	Mast Cell in Masseter Muscle Repair	NIDCR	100,000
	Research Registries and Repository for the Evaluation of TMJ Implants	NIDCR	100,000
Diabetes	Diabetes Prevention Program Outcomes Study	NIDDK	100,000
	Gestational Diabetes and Preeclampsia Cytokine Profiles	NIDDK	100,000
Endocrinology	Estradiol and Hippocampal Development	NINDS	333,155
Gastroenterology	Improving IBS Outcomes	NINR	100,000
Genitourinary	Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome	NIDDK	200,000

* Research titles are listed under broad topical subject areas.

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TABLE 1 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2005

Subject	*Title**	*IC†*	*Award Amount*
	New Tool to Diagnose Female Urinary Incontinence	NICHD	$ 100,000
	Mechanisms of Female Urinary Incontinence in Diabetes	NIDDK	187,555
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	FIC	50,000
	Scale-up of Community-based HIV Prevention and Care	FIC	50,000
	AIDS International Training and Research Program	FIC	50,000
	Brown/Tufts AIDS International Training and Research Program	FIC	100,000
Immunity/ Autoimmunity	Mechanism Regulating Neutrophil Activation in Pregnancy	NIAID	50,000
	Sex-based Differences in the Immune Response	NIAID	50,000
	Predictors of Pregnancy Outcome in SLE and APS	NIAMS	400,000
	Brain Connections	NIAMS	100,000
	Antibodies to NR2 in SLE	NIAMS	80,000
	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
	UCSF Autoimmunity Center of Excellence	NIAID	60,000
	Treatment of Autoimmune Disease by Costimulatory Signal	NIAID	60,000
	Suppression and Exacerbation of B- and T-Cell Response	NIAID	60,000
	Modulation of B-Cell Responses in Autoimmunity	NIAID	60,000
	UAB Autoimmunity Center for Excellence	NIAID	60,000
	Animal Model for Graves' Disease/Ophthalmology	NEI	151,500
	International Research Registry Network for Sjögren's Syndrome	NIDCR	200,000
Infectious Diseases	Seroprevalence/Incidence of Genital Herpes	FIC	20,000
	Natural Antimicrobials against Bacterial Vaginosis	NCCAM	187,678
Menopause	Study of Women's Health Across the Nation (SWAN III)	NIA	250,000
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	200,000
	Soy Isoflavones for Menopausal Vasomotor Symptoms	NCCAM	324,190
Mental Health	Health Survey of Two-spirited Native Americans	NIMH	175,000
	Pharmacogenomics Research Group on Depression	NIGMS	50,000
	NARCH Project on Youth Suicide Prevention	NIGMS	25,000

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TABLE 1 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2005

Subject	*Title**	*IC†*	*Award Amount*
Musculoskeletal Systems	Osteo-Arthritis Initiative (OAI)—Baltimore	NIAMS	$ 67,033
	Osteo-Arthritis Initiative (OAI)—Columbus	NIAMS	524,739
	Osteo-Arthritis Initiative (OAI)—Pittsburgh	NIAMS	208,228
	Low-Dose Doxycycline Effects on Osteopenic Bone Loss	NIDCR	315,644
	Bone-Sparing by Ca Salts with and without Extra Phosphorus	NIAMS	75,000
	Bone-Sparing Effects of Soy Phytoestrogens in Menopause	NIAMS	100,000
Nutrition	National Food and Nutrient Analysis Program	USDA	100,000
	Botanical Supplements for Women's Health	NCCAM	100,000
Obesity/Overweight	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	100,000
	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	75,000
	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	75,000
	Health Outcomes of Weight-Loss—Data Coordinating Center	NIDDK	100,000
Ophthalmic Disease	Incidence of Late Macular Degeneration in Older Women	NEI	230,000
	Estrogen Receptors and Maintenance of Lens Transparency	NEI	132,549
Pain	Hormonal Cycles of Women: Effects of TMD Pain Symptoms	NIDCR	150,000
	Pain Management in TMJD	NIDCR	269,127
	Trigeminal Pain Mechanisms	NIDCR	168,176
	Imaging the Cognitive Modulation of Pain in Fibromyalgia	NIAMS	250,000
Physical Activity	Social Cognitive Theory and Physical Activity after Endometrial Intervention	NCI	100,000
	Young Adult Environment and Physical Activity Dynamics	NCI	100,000
	Mediators and Moderators of Exercise Behavior Change	NCI	100,000
	Angiogenesis and Mechanisms of Exercise Training	NHLBI	100,000
Reproductive Health and Developmental Biology	ORWH-NICHD Leiomyoma Tissue Bank	NICHD	93,000
	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
	Intermediate Outcomes of Hysterectomy and Alternatives	NIEHS	250,000
	Pregnancy and Drug Metabolizing Enzymes and Transporters	NICHD	50,000

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TABLE 1 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2005

Subject	*Title**	*IC†*	*Award Amount*
	Washington Obstetric-Fetal Pharmacology Research Unit	NICHD	$ 50,000
	UW Obstetric-Fetal Pharmacology Research Unit	NICHD	50,000
	Obstetric-Fetal Pharmacology Research Units Network	NICHD	50,000
	Impact of Sex Differences and Pregnancy in Drug Disposition	NICHD	75,000
	Gestational Hypothyroidism	NICHD	25,000
	Development and Differentiation in Reproductive Axis	NICHD	250,000
	Biologic Effects of Androgens in Men and Women	NICHD	200,000
	MMC/PSU Cooperative Center for Research in Reproduction	NICHD	200,000
	Mechanisms of Antibody-induced Pregnancy Loss (aPL)	NIAMS	100,000
	American Indian Women and Childbearing Experiences	NINR	41,527
Violence	Impact of Domestic Violence of Cancer Treatment	NCI	7,936

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TABLE 2
ORWH Co-Sponsored Research Initiatives, FY 2006

Subject	*Title**	*IC†*	*Award Amount*
Aging	Phytoestrogens and Aging: Dose, Time and Tissue	NIA	$ 97,650
	Health, Illness, and Social Life at Older Ages	NIA	244,125
	Calif. Native American Research Center for Health	NIGMS	75,000
	Caregivers' Strengths-skills: Managing Older Cancer Patients	NCI	50,000
Alcohol and Other Substance Abuse	Sex Differences in Opioid Analgesia	NIDA	50,000
	Reducing Alcohol and Risks among Young Females	NIAAA	150,000
	Vulnerability to Drug Abuse and Treatment Efficacy: Animal Models	NIDA	306,356
	Functionality of the Opioid System during Adolescent Development across Genders	NIDA	65,475
Cancer	Clinical Trials of Two HPV-like Particle Vaccines	NCI	1,100,000
	Pharmacogenetics of the Endocrine Treatment of Breast Cancer	NIGMS	244,125
	Patient-centered Communication during Chemotherapy	NCI	48,825
	Iyengar Yoga for Breast Cancer Survivors with Persistent Fatigue	NCCAM	231,749
	Qigong Effects on Fatigue and Cognitive Function after Treatment for Breast Cancer	NCCAM	188,039
Cardiovascular Disease	Genetics of Early-Onset Stroke	NINDS	292,950
	Altered Glucose and Lipid Metabolism in Obesity and CVD	NHLBI	195,301
	Inflammation and Insulin Resistance in Peripheral Arterial Disease	NHLBI	10,000
	Yoga and Indices of Cardiovascular Risk in Older Women	NCCAM	302,999
Chronic Fatigue Syndrome	Autonomic Nervous System in CFS	NINDS	382,500
	Neuropeptide Y and Dipeptidyl-Peptidase IV (CD26) in CFS	NIAAA	152,063
	Risk Factors Associated with CFS	NIAID	97,650
	Cognitive Behavioral Stress Management for CFS	NINDS	343,219
	A Prospective Study of CFS in Adolescents	NICHD	293,000
	Mast Cells, Antidepressants, and CFS	NIAAA	299,875
Craniofacial Disorders	Brief Focused Treatment for TMD: Mechanisms of Action	NIDCR	97,650
	Genotype and TMJD Vulnerability Types	NIDCR	97,650
	Neuronal Plasticity Related to TMJ and Fibromyalgia	NIDCR	97,650
	Estrogen Regulation of Inflammation Related to TMJ	NIDCR	97,650
	Mast Cell in Masseter Muscle Repair	NIDCR	97,650
	Research Registries and Repository for the Evaluation of TMJ Implants	NIDCR	100,000
	Bone Growth in Dental, Cranial, and Skeletal Tissue	NIDCR	19,530

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TABLE 2 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2006

Subject	*Title**	*IC†*	*Award Amount*
	A Systems Approach to the Understanding of a Complex Disease	NIDCR	$ 5,000
Diabetes	Diabetes Prevention Program Outcomes Study	NIDDK	292,950
Gastroenterology	Improving IBS Outcomes	NINR	97,650
Genitourinary	Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome	NIDDK	195,300
	Epigenetics X-Linked Genes in PBC: Does X Mark the Spot?	NIDDK	189,479
HIV/AIDS	Impact of Delivery Models in HIV Health Care	FIC	19,530
	Interventions to Reduce HIV-1 Incidence after Delivery	FIC	19,530
	AIDS International Training and Research Program	FIC	50,000
	Scale-up of Community-based HIV Prevention and Care	FIC	50,000
	AIDS International Training and Research Program	FIC	50,000
	Mentor Mothers: A Sustainable Family Intervention in South African Townships	NIMH	300,000
Immunity/ Autoimmunity	Sex-based Differences in the Immune Response	NIAID	78,120
	Predictors of Pregnancy Outcome in SLE and APS	NIAMS	390,600
	Brain Connections	NIAMS	97,650
	Antibodies to NR2 in SLE	NIAMS	78,120
	EBNA-1 in Lupus	NIAID	195,300
	UCSF Autoimmunity Center of Excellence	NIAID	56,600
	Treatment of Autoimmune Disease by Costimulatory Signal	NIAID	56,600
	Suppression and Exacerbation of B- and T-Cell Response	NIAID	56,600
	Modulation of B-Cell Responses in Autoimmunity	NIAID	56,600
	UAB Autoimmunity Center for Excellence	NIAID	58,600
	IXth International Symposium on Sjögren's Syndrome	NIDCR	5,000
	Immunoregulatory Effects of Estrogen in EAE	NINDS	250,000
	International Research Registry Network for Sjögren's Syndrome	NIDCR	200,000
Infectious Disease	Seroprevalence/Incidence of Genital Herpes	FIC	19,530
Menopause	Study of Women's Health Across the Nation (SWAN III)	NIA	244,125
	Phytoestrogens and Progression of Atherosclerosis	NCCAM	195,300
	Biological Mechanisms of Arterial Stiffening with Age and Estrogen Deficiency	NIA	50,000
	Estrogen: Neuroprotection in the Perimenopause	NIA	50,000

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TABLE 2 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2006

Subject	*Title**	*IC†*	*Award Amount*
	Estradiol Regulation of In Vivo Adipose Tissue Glucocorticoid Metabolism	NIA	$ 50,000
	Menopause: Decreased Response to Increasing Inflammation	NIA	50,000
	Endogenous Neurosteriod Regulation of GABAARS	NINDS	41,796
	Effects of Chronic Estrogen on TIDA Neurons: Roles of Cytokines and NO	NIA	50,000
	Neurobiology of the Menopausal Transition	NIA	50,000
	Impact of Endocrine Aging on Brain and Immune Response	NIA	50,000
	Cytokine Moderation by FSH Hormones	NIA	50,000
Mental Health	Health Survey of Two-spirited Native Americans	NIMH	170,887
	NARCH Project on Youth Suicide Prevention	NIGMS	75,000
	Antimanic Use during Pregnancy	NIMH	200,000
	Modifying MET for Use with ASI Data	NIDA	9,765
	Treatment of Addiction to Nicotine in Schizophrenia	NIDA	9,765
Musculoskeletal Disorders	Osteo-Arthritis Initiative (OAI)—Baltimore	NIAMS	67,033
	Osteo-Arthritis Initiative (OAI)—Columbus	NIAMS	524,739
	Osteo-Arthritis Initiative (OAI)—Pittsburgh	NIAMS	208,228
	Bone-sparing Effects of Soy Phytoestrogens in Menopause	NIDDK	97,650
	Impaired Acyl-CoA Synthetase-Muscle Lipid Oxidation in African American Women	NIDDK	263,625
Microbicides	Identification and Preclinical Testing of Microbicides	NIAID	13,333
	An In Vitro Model of Cell-associated HIV-1 Transmission	NICHD	13,333
	Engineering Semian-derived Lactobacilli to Secrete Anti-HIV-1 Microbicide	NIAID	13,333
	CVN-12p1 Chimeras and Combination for AIDS Microbicides	NIAID	13,333
	Syndecan Agonists and Antagonists as Microbicides	NIAID	13,333
	Implementation of Vaginal/Rectal HIV Transmission Model to Evaluate Microbicide	NIAID	13,333
	Topical Microbicide against HIV and Chlamydia	NIAID	13,333
	Development of Tissue Explant Models for Microbicides Evaluation	NICHD	13,333
	Topical Immune Modulatory Strategies to Prevent HIV Transmission	NIAID	13,333
	Development of N-Peptides for Use in HIV-1 Topical Microbicides	NIAID	13,333
	Linking Biophysical Functions of Microbicides to User Perception and Acceptability	NIMH	13,333
	Recombinant CCR5 Inhibitors for Topical Microbicides	NIAID	13,333
	Proteolytic Antibody HIV Microbicides	NIAID	13,333
	A Topical Treatment for Genital Papillomavirus Infections	NIAID	13,333

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TABLE 2 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2006

Subject	*Title**	*IC†*	*Award Amount*
Nutrition	Botanical Supplements for Women's Health	NCCAM	$100,000
	Bench to Bedside Research Program, Vitamin E Pharmacokinetics and Oxidative Biomarkers in Normal and Obese Women	CC	10,000
	Bench to Bedside Research Program, Alpha-Tocopherol Modulation of Xenobiotic Metabolism	NIDDK	70,750
	ASP 47th Annual Meeting: Natural Products on Target	NCCAM	5,000
Obesity/Overweight	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	97,650
	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	73,237
	PRIDE: Program to Reduce Incontinence by Diet and Exercise	NIDDK	73,237
	Health Outcomes of Weight-loss Data Coordinating Center	NIDDK	97,650
Ophthalmic Disease	Incidence of Late Macular Degeneration in Older Women	NEI	224,595
	Estrogen Receptors and Maintenance of Lens Transparency	NEI	132,549
Pain	Hormonal Cycles of Women: Effects of TMD Pain Symptoms	NIDCR	146,475
	Trigeminal Pain Mechanisms	NIDCR	168,176
	fMRI Measure of Central Sensitization in Migraine	NINDS	255,564
	Refining Diagnostic Criteria of a Pain Disorder: Vulvar Vestibulitis Syndrome	NICHD	139,572
Physical Activity	Social Cognitive Theory and Physical Activity after Endometrial Intervention	NCI	97,650
	Young Adult Environment and Physical Activity Dynamics	NCI	97,650
	Mediators and Moderators of Exercise Behavior Change	NCI	97,650
	Angiogenesis and Mechanisms of Exercise Training	NHLBI	244,125
Reproductive Health and Developmental Biology	ORWH-NICHD Leiomyoma Tissue Bank	NICHD	145,000
	Protein Tyrosine Kinases in Leiomyomata Uteri	NICHD	73,237
	Finding Genes for Uterine Fibroids	NICHD	73,237
	Estrogen Dependency of Uterine Leiomyoma	NICHD	73,237
	Molecular Etiology of Leiomyoma Uteri	NICHD	73,237
	Regulation of Uterine Fibroids by CCN5	NICHD	73,237
	Reactive Oxygen Species Regulate Smooth Muscle Growth	NICHD	73,237
	Leiomyomata Uteri: Apoptosis and Cell Survival Pathways	NICHD	73,237
	Estrogen Biosynthesis and Uterine Leiomyomata	NICHD	73,237
	Intermediate Outcomes of Hysterectomy and Alternatives	AHRQ	244,125
	Pregnancy and Drug Metabolizing Enzymes and Transporters	NICHD	150,000
	Washington Obstetric-Fetal Pharmacology Research Unit	NICHD	50,000
	UW Obstetric-Fetal Pharmacology Research Unit	NICHD	50,000

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TABLE 2 *(continued)*

ORWH Co-Sponsored Research Initiatives, FY 2006

Subject	*Title**	*IC†*	*Award Amount*
	Obstetric-Fetal Pharmacology Research Units Network	NICHD	$ 50,000
	Biologic Effects of Androgens in Men and Women	NICHD	200,000
	MMC/PSU Cooperative Center for Research in Reproduction	NICHD	200,000
	Mechanisms of Antibody-induced Pregnancy Loss (aPL)	NIAMS	97,650
	Functions of Pregnancy Specific Glycoproteins	NICHD	272,700
	Maternal Physiological Factors Influencing Labor Length	NINR	33,582
	Molecular Mechanisms of FOXL2, an Ovarian Failure Gene	NICHD	278,601
	Lactation and Diabetes Risk Factors in Women	NIDDK	236,100
	Supplements to Promote Re-Entry into Biomedical and Behavioral Research Career	NICHD	20,000

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Scientific Highlights from ORWH-Funded Research during FY 2005 and 2006

The portfolio of research that resulted from ORWH investments in FY 2005 and 2006 is extensive. The ORWH and the NIH ICs utilize a variety of funding mechanisms to support these projects, including investigator-initiated grants, such as R01s, R03s, and R21s. However, other mechanisms are used as well, including program project grants and contracts. To stimulate research in specific areas, RFAs and PAs are used. A list of RFAs and PAs related to women's health and sponsored by the ORWH and other NIH ICs in FY 2005 and 2006 is provided in Table 3 below. In addition, a trans-NIH program created by the ORWH called the *Research Enhancement Awards Program (REAP)* also supports meritorious research on women's health that has just missed the institute pay-line for funding.

The following sections highlight some of the research related to women's health. While illustrative of research supported by the ORWH, these examples do not cover the full spectrum of the research portfolio on women's health. The ORWH continues to develop its research base in other areas of programmatic importance and relevance to women. This research addresses health promotion, healthy aging, physical activity, nutritional research, and eating disorders, such as obesity. Through successful collaboration of the ORWH with the NIH ICs, the Office is able to provide funds for research on sex differences in health and disease in many areas, such as irritable bowel syndrome, stroke, treatments for obesity (including bariatric surgery), and the consequences and treatment of substance abuse. Additionally, the ORWH co-funds innovative grants that focus on culture and cancer disparities, end-of-life care, and caregiver research.

Breast Cancer Pharmacogenomics

The ORWH is co-funding a grant with the National Institute of General Medical Sciences (NIGMS) Pharmacogenetics Research Network (PGRN) to investigate tamoxifen in breast cancer treatment. Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but deciding which drug is best for each woman remains unclear. Through a recent series of laboratory and clinical studies, new genetic patterns that predict the effects of the estrogen receptor modulator, tamoxifen, have produced interesting data. Additional studies to build on these data will examine the influence of an extended series of candidate genes on the effects of the class of drugs known as aromatase inhibitors. These studies will refine the genetic signatures that predict tamoxifen's effects.

PGRN research revealed that certain gene variations—and some medicines—can alter the effect of tamoxifen. The new information will improve treatment outcomes by helping physicians and patients choose the appropriate drug. Tamoxifen has been used since the 1970s to treat patients with hormone-dependent breast cancer and, more recently, to ward off the disease in those at high risk for it. The drug works by blocking estrogen's ability to help the cancer grow.

Tamoxifen must be metabolized in the body into its active chemical form to be effective. This is accomplished by several enzymes, including a crucial liver enzyme called CYP2D6. People can inherit different genetic variants of the CYP2D6 enzyme. The most common version (found in about 60 percent of the American population) metabolizes tamoxifen readily. Another variant (found in about 30 percent of Americans) works more slowly.

Clinical studies by PGRN scientists showed that patients with the faster enzyme had a 20 to 25 percent chance of breast cancer recurrence after a decade. In comparison, individuals with the slower enzyme had a 60 percent chance of recurrence. Also important is that tamoxifen's effectiveness can be greatly altered by a patients' genetic makeup and that other chemotherapy agents are available that might work better for some people. This genetic approach may help identify patients who respond very well to tamoxifen.

This research also revealed that some antidepressants, which are prescribed to treat hot flashes and other side effects of cancer therapy, can similarly diminish the effectiveness of tamoxifen. These medicines include paroxetine (Paxil) and fluoxetine (Prozac), both members

of the family of selective serotonin reuptake inhibitors (SSRIs). These antidepressants were found to reduce the activity of CYP2D6, preventing the enzyme from converting tamoxifen into its active form. Doctors now avoid prescribing SSRIs with this effect to people taking tamoxifen.

The results of this research have generated new information that, linked with the novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools that are key to optimizing drug selection for women with breast cancer. The results will also enhance our understanding of the mechanisms of estrogen action.

Human Papillomaviruses (HPV) Vaccine

The ORWH is providing support for National Cancer Institute (NCI) researchers to evaluate the efficacy of a new HPV vaccine in a clinical trial being conducted in Costa Rica. Each year, cervical cancer causes more than 200,000 deaths around the world, making it the second most common cause of cancer mortality worldwide. A wealth of scientific evidence has shown that virtually all cases of this cancer are attributable to cervical infection by a subset of HPV. About one-half of cervical cancers are attributable to cervical infection by a subset of HPV 16 virus. The second most frequent type, HPV 18 virus, accounts for another 10 to 20 percent of these cancers. An effective HPV vaccine should be able to reduce the incidence of cancers attributable to HPV infection.

With support from the ORWH, NCI investigators have developed a method for producing an HPV vaccine composed of a single noninfectious protein from the virus. All women in the randomized clinical trial benefit from excellent cervical cancer screening. The prevention of cervical cancer is the main public health goal of the vaccine. The current vaccine targets HPV16 and 18 viruses, which together account for about 60 to 70 percent of cervical cancer worldwide. If a vaccine is 90 percent effective against these HPV types, it will have the potential of saving 150,000 lives per year. The vaccine would be expected to reduce by about 500,000 the number of precancerous cervical lesions that require treatment, leading to a substantial reduction in morbidity, anxiety, and cost.

Uterine Leiomyoma (Uterine Fibroids)

The ORWH has had a long-standing interest in fostering greater research on uterine fibroids because of the high prevalence of this condition in women of all races and ethnicities, but especially for women of color. Uterine fibroids represent a health disparity that disproportionately affects African American women. During FY 2005 and 2006, the ORWH collaborated on a number of important projects in this area.

With support from the ORWH and the National Institute of Child Health and Human Development (NICHD), the Leiomyoma Tissue Bank (LTB) was created in FY 2005. Research into the causes and treatment for fibroids has lagged behind other disciplines, in part due to a lack of available tissues. To address the problem of tissue availability and to promote research on this condition, a tissue bank was established to provide samples to investigators funded by the NIH and the Department of Defense (DoD) to support work on this condition. The LTB is located in the NICHD and is structured after similar banks created for endometrium and ovary tissue established by the Specialized Cooperative Program in Reproductive Research.

The NICHD and the ORWH are co-funding several extramural research projects that address the molecular basis of uterine fibroids. The ORWH and the NICHD also co-funded eight grants on uterine fibroids focusing on basic science and translational research. Research has confirmed that uterine fibroids are extremely prevalent with severe morbidity seen in many women and are an area of interest for health disparities since they are more prevalent in certain subpopulations of women. Similarly, hysterectomies, which are performed for this condition, disproportionately affect these subpopulations of women. Therefore, research is addressing the gaps in knowledge about the pathobiology of uterine fibroids and better ways to treat them. The ORWH also funded a study with the AHRQ to delineate alternatives to hysterectomy to better understand ways to reduce this very common surgical procedure.

The ORWH, the National Institute of Environmental Health Sciences (NIEHS), and the NICHD took the lead in planning and convening the 2005 *NIH Conference on Advances in*

Uterine Leiomyoma Research: Second NIH International Congress. Of significance, this conference was co-sponsored by several NIH ICs and Offices, including the NIEHS, the NICHD, the NCI, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Center for Research Resources (NCRR), and the ORWH as well as other agencies, including the FDA, the AHRQ, the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and the DHHS OWH. The goal of this conference was to bring together researchers working in the fields of biomedicine, epidemiology, basic sciences, therapeutics, and translational medicine to foster an exchange of scientific information among members of the uterine leiomyoma research and health care communities. Participants were drawn from academia, medical centers, government, and industry. Topics discussed at the conference included clinical experience and therapeutic strategies, epidemiology, clinical trials, pathogenesis of smooth muscle tumors, and molecular and genetic characteristics. The full summary of the conference and conference link are available online at http://orwh.od.nih.gov/health/uterinefibroidmtg.html.

Vulvodynia

The ORWH, the NICHD, other components of the NIH, public advocacy groups, and other agencies in the DHHS are collaborating on efforts to advance research and education on vulvodynia. Vulvodynia is defined as chronic discomfort or pain of the vulva. This discomfort has been referred to in a variety of terms, such as "the pain down there" or "feminine pain." It is a type of pelvic pain that may be acute or chronic. This clinical syndrome of unexplained vulvar pain may result in sexual dysfunction. The burning, stinging, or irritated feeling can be in a small area or generalized to the whole vulva. There is no apparent infection or skin disease that could cause these symptoms. No single treatment is effective for all cases, but a multifaceted approach to prevent and reduce irritation can be taken to improve quality of life.

Studies on the epidemiology of vulvodynia have helped to clarify the magnitude of the problem. A large population-based study in ethnically diverse Boston neighborhoods, co-funded by the ORWH, revealed that chronic burning, knife-like pain, or pain on contact that lasted at least three months or longer in the lower genital tract, occurred frequently in white, African American, and Hispanic women (Harlow, B.L. and Stewart, E.G. *Journal of the American Medical Women's Association* 58:82-88, 2003). Nearly 40 percent of these women chose not to seek treatment. Of the women who sought treatment, 60 percent saw three or more doctors. Investigators conservatively estimate that at least 9 percent of women will experience symptoms consistent with vulvodynia in their lifetime. These findings highlight the reality that vulvodynia affects many women in the U.S. and that women who suffer from vulvodynia may not know about the possibilities for treatments. When women do choose to seek care, the lack of provider training for diagnosis and treatment may lead to multiple office visits with different health care providers.

Today research continues to explore improved clinical definitions of vulvodynia, improved methods of identifying conditions that coexist with vulvodynia, and improved comprehensive clinical management tools. Findings from NIH-funded research have led to several active research PAs. One PA issued by the NICHD and co-sponsored by the ORWH was titled Vulvodynia—Systematic Epidemiologic, Etiologic or Therapeutic Studies (PA-06-302). Designed to promote interdisciplinary research, its goal is to reduce the burden of this disorder and ultimately to improve the quality of life for women affected by vulvodynia.

In addition to funding scientific research for this disorder, the NICHD with the ORWH has funded a series of workshops on the epidemiology, basic science, pain research, evolving therapies, and therapeutics associated with vulvar pain. NIH participated in the most recent workshop, which was co-chaired by the ORWH Director and was recently published in an article titled *Vulvodynia: A State-of-the-Art Consensus on Definitions, Diagnosis and Management* (Bachmann G.A., Rosen R, Pinn VW, et al. *Journal of Reproductive Medicine* 2006;51 (6): 447-56). This publication describes findings and recommendations, such as key topics and issues needing urther study, including the role of inflammatory mechanisms and genetic factors.

For research on vulvodynia to progress, definitions should be standardized for the terms that describe vulvodynia and the conditions that are associated with it. The terms and procedures used to characterize the pain associated with vulvodynia should also be standardized. Many biological mechanisms are currently being investigated, including inflammatory and infectious disease processes, stress factors, neurologic and genetic factors, and the relationships between these processes and hormonal and immune system changes. Establishing the natural progression of vulvodynia will contribute toward a better understanding of the role of etiologic factors (causes).

The NIH will continue to foster and support research and coordinate educational efforts for patients and health care providers based on research and scientific evidence on vulvodynia. To further outreach efforts, ORWH and its partners are developing a national educational program for primary health care providers, patients, and the general public regarding the symptoms, diagnosis, and treatment options of vulvodynia. Current information on vulvodynia is available at the ORWH Web site at http://orwh.od.nih.gov/health/vulvodynia.html.

Menopause-related Research

The ORWH supports an extensive research portfolio on many aspects of the menopausal transition and symptoms. In FY 2006, the ORWH supported a National Institute on Aging (NIA) RFA on the Biology of the Perimenopause: Impact on Health and Aging in Non-Reproductive Somatic and Neuronal Tissues (RFA-AG-05-008), from which several grants were awarded.

This RFA solicited applications for research studies to better understand underlying biologic mechanisms associated with the menopausal transition in middle-aged women. The NIH was most interested in studies relating to how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within non-reproductive somatic and neuronal target tissues. Other scientific areas of interest included the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause and the role of aging on these pathophysiologic processes.

Research projects from this RFA funded in FY 2006 included studies looking at women across the menopausal transition or biospecimens from that group of women. These studies will focus on the roles of estrogen and glucocorticoids in abdominal adiposity and skeletal and vascular health; the effects of cytokine secretion under FSH regulation; the role of estrogen and age in arterial stiffening; and the patterns of brain activation during cognitive and emotional tasks. A second group of studies will utilize an animal model (female rodents) undergoing reproductive aging. These animal studies will focus on how reproductive aging and estrogen modulate the inflammatory environment of the brain and periphery; the estrogen-sensitive neuronal systems of the hypothalamus and effects on prolactin secretion; the survival and function of hippocampal neurons in collaboration with IGF-1 in a global ischemia model; and the transcriptional activation of estrogen receptors by non-estrogenic activators, as well as estrogen.

The ORWH also co-funded other menopause-related grants with the National Institute on Aging (NIA), the National Center for Complementary and Alternative Medicine (NCCAM), and the National Institute of Mental Health (NIMH). These studies include the Study of Women across the Nation (SWAN), 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 health care providers and women across different racial and ethnic groups. Other menopause-related research includes an ongoing study on menopausal depression, which is funded by the NIMH with support from the ORWH. The ORWH, the Office of Dietary Supplements (ODS), and the NCCAM are partnering on several grants that focus on botanical products or other complementary and alternative medicine (CAM) methods to treat symptoms associated with the menopause. Additional areas of focus include the effects of botanical products on a woman's cognition and on the progression of atherosclerosis, which is a major disease outcome in postmenopausal women.

The NIH State-of-the-Science Conference on Management of Menopause-related Symptoms

In March 2005, the NIH's Office of Medical Applications of Research (OMAR) conducted a State-of-the-Science (SoS) conference on menopause-related symptoms. The primary sponsor of this conference was the NIA, although other components of the NIH and other federal agencies, such as the ORWH, the NCCAM, the NCI, the National Heart, Lung, and Blood Institute (NHLBI), the NICHD, the NIMH, the FDA, and the OWH (DHHS, co-sponsored this meeting.

The independent panel convened at this conference found that many women move through the menopausal transition with few disabling symptoms. It was noted that it is important for menopause to not be viewed as a disease. The tendency among women and their health care providers in the U.S. to "medicalize" menopause concerned the panel because the tendency can lead to overuse of treatment approaches that are known to carry serious risks or whose safety remains unclear.

However, many women, particularly those with surgically induced menopause, do experience significant symptoms that greatly diminish quality of life. For women whose menopausal symptoms are severe and persistent, the panel found nothing as effective as estrogen therapy for alleviating those symptoms. Low-dose estrogen has been shown to be effective for many women, although some require larger doses to relieve hot flashes. Concerns about the risks associated with estrogen use may rule out this treatment option for some groups of women. The panel cautioned women to weigh carefully their personal risks and potential benefits before starting treatment, noting that for some women whose symptoms create a serious burden on daily life, the benefits of symptom relief may outweigh the risks. In addition to learning more about the safe use of hormones, the panel urged further research into non-hormonal treatment approaches.

The panel also found that, overall, there have been very few well-designed studies to evaluate the safety and effectiveness of CAM approaches to menopausal symptom management, including behavioral interventions. Although many studies have been published, most have important limitations that make their findings unclear. The evidence on most botanical products used or advocated for treating menopausal symptoms is weak or inconsistent. There are major methodological problems associated with products that are not standardized.

More information on the SoS conference is available online. The final version of the conference report can be found at http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025html.

Prevention Research

While prevention has always been a component of the ORWH research portfolio, in FY 2005, the Office began to place special emphasis on prevention-related research in women's health. The following key programs were begun in FY 2005 and 2006.

Microbicides Innovation Program (MIP)

The ORWH, in collaboration with the NIH Office of AIDS Research (OAR), the National Institute of Allergy and Infectious Diseases (NIAID), the NICHD, and the NIMH, has funded a number of R21/R33 innovation projects to support exploratory and developmental research on new microbicides and microbicides strategies and technologies. The goal of this program is to advance promising strategies and technologies into preclinical and clinical development of new agents.

The development of safe, effective acceptable topical microbicides to prevent the sexual transmission of HIV could play a major role in worldwide reduction of new HIV infections. An effective and acceptable microbicide potentially could save millions of lives. Topical microbicides are agents that when applied vaginally, rectally, or on the penis can result in inhibition of the transmission of HIV and/or other sexually transmitted infections (STIs), which may be cofactors in HIV transmission. Although no licensed microbicide is currently available, large-scale effectiveness trials of five candidate microbicides are underway, including an NIAID-sponsored trial that opened in February 2005.

The purpose of the MIP is to support novel and underexplored strategies in the field of topical microbicides. This broad-based

program will support the development of microbicides and will facilitate technology or methodology design and development that may advance the field as a whole. The MIP supports four areas of research. First is the discovery and exploration of microbicides (singly or in combination) directed against HIV and/or STIs linked to HIV acquisition. These include, but are not limited to, herpes simplex virus (HSV), *Trichomonas vaginalis*, *Treponema pallidum*, HPV, *Haemophilus ducreyi*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *bacterial vaginosis*. The second area is looking at emerging technologies or models that contribute to new and/or more efficient mechanisms for assessing microbicide safety, efficacy, and acceptability; discovery and exploration of new microbicide candidates; formulation and delivery of microbicide products; and validation of surrogate markers for safety and/or efficacy. The third area includes prevention strategies that incorporate vaginally, rectally, and/or penile-applied microbicides. Acceptable strategies may include anti-HIV vaccines that block HIV transmission at the vaginal or rectal mucosa as an adjunct to the primary microbicide approach. The fourth area addresses the development of behavioral and social tools that focus on product acceptability, initiation of use, and potential for sustained use. These tools must be designed to be integrated into the preclinical development of microbicides. They should allow iterative steps to improve the product or strategy under investigation. Success of these tools will hinge on behavioral, cultural, and contextual factors (e.g., product characteristics, perceived risk of infection, partner cooperation, and the like).

OTHER PREVENTION-RELATED RESEARCH

The ORWH supports a number of research projects related to the prevention of diseases and disorders of importance to women. For example, the ORWH is co-funding a National Institute on Alcohol Abuse and Alcoholism (NIAAA) grant to reduce alcohol consumption among urban Latina and African American adolescent girls by educating parents to the dangers associated with alcohol abuse. Three alcohol prevention interventions are being tested, and both parents and their daughters will be monitored over several months. The ORWH, in collaboration with the Fogarty Internal Center (FIC), has funded a number of projects that focus on HIV/AIDS prevention in international locations, including Colombia, Africa, and Haiti.

Colombia, which ranks fourth in the total number of reported HIV cases in Latin America, is evaluating the utilization and cost implications of different health care delivery models in Bogota, Colombia. Data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase of this study, 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 highly active anti-retroviral therapy (HAART). 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.

Other projects focus on African locations, including Kenya. Women in sub-Saharan Africa face a high risk of HIV-1 acquisition during the first year postpartum. This risk can be reduced by antenatal voluntary counseling and testing (VCT) and use of 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. This study is determining 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 in three sites in Kenya. 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.

Another project focuses on training Haitian scientists in biomedical, epidemiological, and biosocial research related to HIV prevention and treatment and the care of individual

patients with HIV in rural Haiti. 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 tuberculosis (TB) and sexually transmitted diseases, the prevention of opportunistic infections, and the use of HAART. The overall program goal of this grant is to provide training that will increase local capacity to perform research on service integration as well as diagnosis and treatment of HIV in central Haiti. Long-term benefits will include increases in research capacity for future HIV-related research activities in Haiti.

Chronic Pain Syndromes

Among the chronic pain syndromes of importance to women's health are temporomandibular joint and muscle disorders (TMJD) and painful bladder syndrome. The ORWH collaborates with a number of NIH ICs to increase research in chronic pain and pain control as important areas for women's health research. The ORWH, the National Institute of Dental and Craniofacial Research (NIDCR), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) co-funded several grants and contracts in the area of chronic pain syndromes. For example, the ORWH and the NIDCR funded several TMJD grants, including 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 TMJD. Additionally, the ORWH co-funded with NIDCR a number of grants addressing such topics as estrogen regulation of inflammation related to TMJD, genotype and TMJD vulnerability types, and neuronal plasticity related to TMJD and fibromyalgia. In FY 2005, the NIDCR and the ORWH co-funded the newly created International Research Registry Network for Sjögren's Syndrome.

The ORWH and the NIDDK have funded a project titled The Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome. Interstitial cystitis 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 interstitial cystitis in the population, the full burden of this syndrome for patients, the kinds of care they seek, and the kinds of treatment they receive. The lack of information about interstitial cystitis makes it difficult to meet patients' needs for medical and non-medical care. Therefore, this project established a case definition of interstitial cystitis in women for patient screening and epidemiological studies; developed and validated a symptom questionnaire that can be used to identify female interstitial cystitis patients and distinguish them from those with similar conditions (e.g., overactive bladder, urinary tract infection, and endometriosis); developed an interstitial cystitis-specific measure of self-reported functional status, including physical, mental, social, sexual/relationship, role functioning, and other factors identified by interstitial cystitis patients as important; and surveyed more than 300,000 women for urinary symptoms. Using the validated symptom questionnaire, the study screened more than 23,000 women to estimate prevalence of interstitial cystitis in the U.S. and to provide a sample of 354 women over age 18 who fit the case definition for this condition and 300 who have interstitial cystitis-like symptoms. This study also described the impact of interstitial cystitis on patients' lives, including interstitial cystitis-specific functional status and the impact of this syndrome 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. Investigators have compared these results with existing data on disease burden for other chronic diseases.

Health Disparities Research

Despite overall improvement in the health of Americans, striking differences exist in the burden of illness, life expectancy, and mortality rates among African Americans, Hispanics, Native Americans, Alaska Natives, Pacific Islanders, and other subpopulations. These differences are thought to reflect complex interactions among biological factors, the environment, and health behaviors. Access to health care resources and socioeconomic differences have also been implicated in

discussions of health disparities. The ORWH and many other componets of the NIH have worked diligently to identify critical research questions and to support research that will help overcome disparities in health, especially as they pertain to women.

The ORWH has funded a number of projects that fall under the category of health disparities research, such as chronic pain syndromes, autoimmune diseases, and musculoskeletal disorders, and projects that focus on under-served, under-represented minorities such as Hispanics and Native Americans. However, the Office also contributes to research on other diseases that differentially affect minority women. An example of one major area is diabetes, which differentially affects women of color, especially African American women. The ORWH has co-funded the Diabetes Prevention Program (DPP) since it was created. During FY 2005 and 2006, the DPP focused on the DPP Outcomes Study (DPPOS). The original DPP looked at the efficacy of lifestyle modification and use of the drug, metformin, to decrease the incidence of diabetes in an ethnically diverse population at high risk for diabetes. The study followed participants for an average of 2.8 years. However, many important questions remain unanswered. Specifically, we do not know whether the decrease in the development of diabetes can be sustained. Moreover, we do not know whether the delay or prevention of diabetes will translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease since these outcomes require more followup years to detect them than the DPP afforded. Thus, a longer-term followup study of the DPP, the DPPOS, was designed to evaluate the long-term effects of active DPP interventions. This study will look at the development of diabetes during a further five to 11 years of followup as well as composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both continued lifestyle intervention and metformin will continue to decrease the rate of diabetes development when compared with the placebo group and that the prevention or delay of diabetes during the DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status. The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

Other research related to health disparities includes several grants to minority institutions co-funded with the NICHD through the Cooperative Reproductive Sciences Research Program. 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. The ORWH also partners with the 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. The ORWH participates with the DHHS Indian Health Service on a youth suicide prevention project that includes capacity building within the local Native American community and research development collaborations.

Autoimmune-related Research

Since its early years, the ORWH has co-funded a number of grants with the NIAID to advance the understanding of the underlying causes, complications, and treatment strategies for autoimmune disorders. More recently, the ORWH co-funded five Autoimmune Centers of Excellence 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 for different autoimmune conditions. As a focal point for women's health research at the NIH, the ORWH continues to encourage greater attention to autoimmunity and its impact on women of all ages, races, and ethnicity. The ORWH also participates in 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 the NIAID, the ADCC is charged with coordinating and monitoring progress in autoimmune research across the NIH, and,

during FY 2005, the ADCC submitted a report to Congress on its progress.

Partnering with the NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Eye Institute (NEI), the ORWH co-funds a number of other autoimmune grants that focus on a number of 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. The ORWH has had a longstanding commitment to provide funding for SLE because of the complex and serious manifestations of this disorder, which is nine times more common in women than men and particularly prevalent in women of color. The ORWH and the NIAMS co-funded several grants exploring the neuropsychiatric manifestations of SLE from a genetic perspective, with the goal of studying the underlying etiology and progression that may lead to the subsequent identification of innovative treatment strategies.

In FY 2005, the ORWH and the NIAMS co-funded an important 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. Thrombosis and pregnancy loss are common features of 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. This research represents a first 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). Similarly, no study has compared pregnant women with SLE with disease-free women to understand whether particular patterns of complement activation characterize and distinguish these patients without aPL antibodies or fetal loss to those with a normal pregnancy. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable physicians 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.

Musculoskeletal Disorders

Musculoskeletal conditions, such as osteoarthritis and osteoporosis, contribute significant disability to women of all ages, but they are especially problematic to women who are postmenopausal. The ORWH has been a long-term partner and co-funder with the NIAMS, NIA, and others in a public-private partnership supporting the Osteoarthritis Initiative (OAI). The OAI is a multicenter, longitudinal, prospective, observational study of knee osteoarthritis. The OAI has successfully recruited 5,000 male and female study subjects. The OAI is serving as a national repository for biological materials about the natural history of osteoarthritis and the evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. These data will eventually 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 for women. In addition, as men are living longer, osteoporosis is increasingly important for aging men. Therefore, it is important to study osteoporosis in both men and women for sex and gender differences as well as for differences among various races and ethnic populations. The ORWH supports several grants with the 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.

Long-term Scientific Collaborations

Most studies receive support from the NIH for three to five years. However, some types of research, such as studies on the natural history of disease or clinical trials requiring longer

term followup, require sustained support for a much longer period of time.

The ORWH has been a collaborator with the NICHD since the introduction of the Obstetrical Pharmacology Research Network, which consists of four clinical research centers and a data coordination center. The network carries out pharmacology research to enhance understanding of obstetrical pharmacokinetics and to improve appropriate therapeutics during pregnancy.

The ORWH has also been a long-term partner with the NIDDK in the weight and incontinence network now known as the Program to Reduce Incontinence by Diet and Exercise (PRIDE). PRIDE is examining the efficacy of weight loss using a cognitive behavioral intervention for six months on incontinence in overweight women, with longer term followup of weight loss maintenance.

The ORWH has collaborated with the NICHD and other ICs since the initiation of the National Longitudinal Study of Adolescent Health (Add Health). As of FY 2006, Add Health is in wave four of data collection. At the time the project began in 1994-1995, investigators selected a nationally representative sample of adolescents in grades seven through 12. Participants have been followed through adolescence and the transition to adulthood with three in-home interviews. Wave four will be the fourth series of interviews and will include additional information that encompasses social, behavioral, and biological data. In addition to data contributed in earlier surveys, these subjects, who are now between the ages of 23 and 31 years, will provide biological data to capture the prevailing health concerns as well as biological markers of future chronic health conditions.

TRANS-NIH COLLABORATION: CHRONIC FATIGUE SYNDROME

The NIH recognizes the enormous complexity involved in studying and treating complex, multisystem illnesses, such as CFS. The NIH also appreciates the need to approach these conditions not simply from the perspective of a single discipline but rather from an interdisciplinary perspective that integrates diverse scientific fields. Because CFS involves systems included in mission statements of a range of NIH ICs and because the research calls for an interdisciplinary perspective, the NIH research on CFS is coordinated in the NIH Office of the Director by the ORWH. This is a familiar role for the ORWH. Since its inception in 1990, the ORWH has been a facilitator of several trans-NIH initiatives for a number of complex conditions affecting the health of both men and women. Through September 1999, the NIAID held sole responsibility for research on CFS. In October 1999, then NIH Director, Dr. Harold Varmus, in consultation with NIAID Director, Dr. Anthony Fauci, recognized that an interdisciplinary and integrated approach encompassing the missions of many NIH ICs was necessary to address CFS. Thus, the responsibility for the CFS efforts was transferred to the NIH Office of the Director. Dr. Donna Dean was appointed to coordinate the NIH efforts. One of the first activities of this centralized activity was to respond to a GAO Report, *Chronic Fatigue Syndrome: CDC and NIH Activities Are Diverse but Agency Coordination is Limited* (GAO/HEHS-00-98). An NIH working group on CFS was established. Dr. Dean also served as co-chair of the DHHS CFS Coordinating Committee. Under her direction, the ORWH sponsored a state-of-the-science symposium on CFS in October 2000.

In April 2001, the ORWH assumed responsibility for coordinating the NIH CFS research efforts. The goal of the ORWH effort is to stimulate interdisciplinary research on CFS. This has been accomplished through a Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG), which is chaired and convened by ORWH staff. The CFSWG is composed of members from 13 different NIH ICs, including the NIAID, NINDS, NHLBI, NIAMS, NIMH, NICHD, and NCRR. (See Appendix D for a list of members.) This working group developed an action plan to draw the attention of the intramural and extramural scientific communities to enhance CFS research at the NIH.

CFS is a debilitating and complex syndrome that involves many 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 than they did before the syndrome began. Neither a specific cause nor treatment has been identified for this illness; there is no diagnostic test for this syndrome. It is possible that multiple subcategories of conditions are subsumed under the rubric of CFS. 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 or racial groups, epidemiologic studies point to gaps in our understanding of the distribution of this syndrome. It is also important to note that 80 percent of people reporting a history of CFS in epidemiologic studies of the general population 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 CDC to have an economic burden resulting from lost productivity of $9.1 billion. This figure is comparable to losses from digestive, immune, and nervous system diseases.

To address the range of important research issues related to CFS, the CFSWG issued a program announcement based on the recommendations from the 2000 state-of-the-science conference on CFS. The CFSWG updated and reissued this announcement in 2005, incorporating recommendations from a June 2003 NIH workshop titled *Neuro-Immune Mechanisms and Chronic Fatigue Syndrome: Will Understanding Central-Mechanisms Enhance the Search for the Causes, Consequences, and Treatment of CFS?* The proceedings of this workshop were published in 2004 (NIH Publication No. 04-5497) and disseminated widely among the scientific communities. All documents mentioned above as well as additional information about the NIH CFS program are available online at http://orwh.od.nih.gov/cfs.html. In addition, the ORWH and the working group issued an RFA (RFA-OD-06-002) that called for research on how the brain, as a mediator of various systems, fits into the schema for understanding CFS. This solicitation specifically called for proposals from interdisciplinary teams of scientists to conduct research on CFS in men and women across the life span. It resulted in seven new research projects that started in 2006 with support from the ORWH, NIAAA, NIEHS, NIAMS, and NINDS. These included two studies co-funded by the ORWH and the NIAAA. One study explores the role of human mast cells in the development of this syndrome and the effects of antidepressants in relieving associated symptoms. The other study is looking at specific peptides (i.e., neuropeptide Y and dipeptidyl-peptidase) that regulate many physiological and disease processes in the cardiorespiratory, immune, nervous and endocrine systems. This research may lead to the development of biomarkers for symptoms of CFS and perhaps their severity. The ORWH is fully funding two studies that are being managed by the NINDS. One will explicate the role of the sympathetic nervous system in the cardiovascular and inflammatory abnormalities in the subset of CFS patients with postural tachycardia (POTS). That study will also examine the relationship between the common mechanisms underlying both CFS and POTS symptoms in a comprehensive set of experiments with appropriate controls. It is hoped that this research will lead to a treatment for CFS symptoms. The other study will test the physiological effects of a telephone-based cognitive-behavioral stress management intervention on participants with CFS. This study also hopes to identify biologically useful markers of CFS. In addition, other NIH ICs (NIAMS, NIEHS, NINDS) are fully funding research from the RFA on CFS.

The ORWH also provided support for other research on CFS that was ongoing during FY 2005 and 2006. For example, the NICHD, with co-funding from the ORWH, has a five-year prospective study of adolescents that will elucidate the etiology and natural history of postviral CFS. The ORWH also provides support for an NIAID study on risk factors associated with the development and prognosis of CFS in an ethnically and socioeconomically diverse sample. This research should elucidate the natural history of this syndrome and lead to improvement in both the diagnosis and treatment of CFS.

The ORWH takes an active role in providing information to the scientific and lay communities on CFS. It continues to maintain and update the CFSWG page on its Web site. The Office inaugurated its Science Series for the Public with a CFS fact sheet. The ORWH also continues to serve as the NIH representative on the DHHS Chronic Fatigue Syndrome Advisory

TABLE 3

Request for Applications and Program Announcements Sponsored by ORWH, FY 2005 and 2006

AIDS International Training and Research Program
(FIC, NCI, NIAAA, NIDCR, NIMH, NIDA, NINR, ODS, ORWH) (PAR-05-140)

Basic Research in the Bladder and Lower Urinary Tract (R01)
(NIDDK, NCI, NIA, ORWH) (PA-06-254)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH III)
(ORWH, NICHD, NIAAA, NIAID, NIDA, NIDDK, NIEHS, NIMH, ODS, AHRQ) (RFA-OD-05-002)

Building Interdisciplinary Research Careers in Women's Health (BIRCWH IV)
(ORWH, NICHD, NIA, NIAAA, NIAID, NIDA, NIMH, NIAMS, AHRQ) (RFA-OD-06-004)

Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01, R21, R03)
(ORWH, ODS, OBSSR, NCCAM, NIAAA, NIAID, NIAMS, NICHD, NHLBI, NIEHS, NINR, NINDS, NIDCR, and NIA) (PA-05-030)

Community Participation in Research (R01, R21)
(OBSSR, NCI, NHLBI, NICHD, NIDCR, NIEHS, NINR, NIAAA, NIMH, NIDCD, NIDA, ORWH, AHRQ, NIOSH, CDC) (PAR-05-026)

Global Research Initiative Program, Behavioral/Social Sciences (R01)
(FIC, NEI, NIDA, NIEHS, NIGMS, OBSSR, ODS, ORWH) (PAR-05-082)

Health Disparities among Minority and Underserved Women (R01)
(NINR, NICHD, NIDA, NIDDK, ORWH) (PA-04-153)

Neuroimmune Mechanisms and Chronic Fatigue Syndrome
(NIAAA, NIAMS, NIEHS, NINDS, OBSSR, ORWH) (RFA-OD-06-002)

NIH Clinical Trial Planning Grant Program (R34)
(NIA, NIAAA, NIAMS, NICHD, NIDCD, NIDA, NINDS, NEI, ORD, ORWH) (PA-06-363)

NIH Support for Conferences and Scientific Meetings (Parent R13/U13)
(NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NCCAM, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NLM, NCRR, NCMHD, ODP, OBSSR, ORD, ODS, ORWH) (PA-06-041)

Pathophysiology of Bisphosphonate-Associated Osteonecrosis of the Jaw (R21, R03)
(NIDCR, NIAMS, NCI, ORWH) (PA-06-501)

Research on Sleep and Sleep Disorders (R01)
(NHLBI, NCSDR, NIA, NIAAA, NCI, NICHD, NCCAM, NIDA, NIMH, NINDS, NINR, ORWH) (PA-05-046)

Research on Social Work Practice and Concepts in Health (R21, R03)
(NCI, NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINR, OBSSR, ODP, ORWH) (PA-06-082)

Sarcoidosis: Research into the Cause of Multi-Organ Disease and Clinical Strategies for Therapy (R01)
(NHLBI, NIAID, NIAMS, NEI, NIDDK, NINDS, NINR, ORD, ORWH) (PA-06-123)

Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50)
(ORWH, NIAMS, NICHD, NIDDK, NIDA, NIEHS, NIMH, FDA) (RFA-OD-06-003)

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

Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms (NIDCR, NIDCD, NINDS, NIAMS, ORWH) (PA-06-188)

Vulvodynia – Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R01) (NICHD and ORWH) (PA-06-302)

Committee. It is expected that continued cooperative efforts to plan and publish interdisciplinary initiatives at the NIH will attract new researchers to the field of CFS. The many NIH ICs working on CFS will continue to encourage and fund CFS-associated research that falls within their purview.

Interdisciplinary Programs

As science has evolved over the past decade, the questions investigators are asking have become more complex. A comprehensive approach to women's health and studies on sex/gender differences is needed to bring together individuals representing different clinical specialties, different scientific backgrounds, and different perspectives to build synergetic collaborations to address complex research questions and to provide better care for women. Interdisciplinary research can facilitate the integration of basic science, clinical research, and translational research and can include population studies, behavioral and social research, as well as health services and outcomes research, bioengineering and biomedical informatics, genomics, proteomics, imaging, and metabolomics. Interdisciplinary research may provide an opportunity for not just medical specialties but also researchers in dentistry, pharmacy, nursing, biotechnology, social sciences, anthropology, genetics, and other disciplines, such as informatics, physics, chemistry, kinesiology, nutrition, and environmental sciences. Women's health provides rich areas for collaboration and synergy of efforts that investigators might explore through interdisciplinary research. Additionally, the pooling of senior investigators across interrelated disciplines creates a rich environment for mentoring of less experienced investigators.

There exists an appreciation of the value that interdisciplinary research provides; this is echoed in many scientific venues. The ORWH saw a need for an interdisciplinary approach to research on women's health and sex/gender issues, and initiated several innovative programs in interdisciplinary research and career training: Building Interdisciplinary Research Career in Women's Health (BIRCWH) and Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health. Both programs have shown benefits to both women's and men's health through sex and gender research and provided opportunities for interdisciplinary scientific collaborations and support for early investigators in a mentored environment to become independent researchers in women's health.

The ORWH also began a trans-NIH interdisciplinary collaboration on women's health and sex/gender comparison research through the establishment of the Intramural Program on Research on Women's Health (IPRWH). The Women's Health Special Interest Group (WHSIG) sponsors bimonthly lectures by NIH and extramural researchers. (See also the Outreach section of this report.) The WHSIG also encourages scientific exchange and multi-institute collaboration, sharing of laboratory resources and equipment, and development of a network to allow brainstorming of ideas for collaboration.

Building Interdisciplinary Research Careers in Women's Health (BIRCWH)

The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program began in 2000 and continues in FY 2005 and 2006. It 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.

Program grants from the BIRCWH RFA provide opportunities to institutions involved in clinical, health, or life sciences or public health departments, centers, and institutes to build a national supply of investigators in women's health research, including research on sex and/or gender differences. The program also affords an opportunity to conduct research on factors that contribute to disparities in health status or health outcomes for different populations of women. As of October 1, 2006, 35 BIRCWH centers have produced 287 scholars that have gone on to receive other 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 the Interdisciplinary Women's Health Research (IWHR) scholars. Mentors from collaborating departments are encouraged to provide needed expertise and resources if the emphasis of IWHR scholars' projects is on research relevant to women's health. Projects can focus on basic, translational, clinical, or health services research, but they must be within the biomedical and behavioral purview of the NIH and/or the health services research purview of the AHRQ. (See Table 3 for a list of BIRCWH solicitations for FY 2005 and 2006 and participating NIH ICs and Offices.) 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.

BIRCWH I (2000-2005)

The ORWH, along with nine NIH ICs and the AHRQ, supported 12 new programs for developing faculty scholars in interdisciplinary women's health research. Several NIH ICs participated in the initial solicitation for the BIRCWH program (RFA-OD-99-008), including the ORWH, the National Institute on Drug Abuse (NIDA), NIA, NIAAA, NIAID, NIAMS, NCI, NICHD, NCCAM, NIDCD, NIDCR, NIDDK, NIEHS, NINDS, and AHRQ. To encourage involvement in the program, sites recruit their own scholars. The BIRCWH I programs included:

Baylor College of Medicine
Houston, TX
PI: Haleh Sangi-Haghpeykar, Ph.D.

The Baylor program offers two tracks: molecular/clinical and clinical/health services/population research. Under this framework, 26 mentors from the 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 work toward a master's degree in a relevant area (e.g., public health). Continued guidance is provided to scholars after completing the program.

University of Alabama at Birmingham
Birmingham, AL
PI: John Hauth, M.D.

The program at Birmingham focuses on the health problems that are 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 are sought. The individualized curricula take into account participants with limited experience as well as those appropriate for an advanced track. The program has a total of 24 mentors, with seven from obstetrics-gynecology form a subgroup on reproductive health. The remaining 17 mentors comprise a diverse group from 11 departments.

University of California–Los Angeles
Los Angeles, CA
PI: Gautam Chaudhuri, M.D., Ph.D.

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

University of California–San Francisco
San Francisco, CA
PI: Deborah Grady, M.D.

The UCSF and the Northern California Kaiser Division of Research joined 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 disease, 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, CT
PI: Judith Fifield, M.D.

Twenty-one women's health investigators, who were scattered across the three campuses of the University of Connecticut, joined as mentors for this program at the Farmington campus. The mentors reflect several disciplines, including allied health professionals. Areas of research in this program include bone and skeletal biology, addictions, mental health, reproductive health and sexually transmitted diseases, and gender roles. Basic, clinical, and sociobehavioral approaches are applied in all these areas. Curriculum and research plans are individualized within three tracks: experienced investigator, limited research experience, and participants with a master's degree (M.P.H. or Master of Dental Sciences).

University of Kentucky
Lexington, KY
PI: Claire Pomeroy, M.D.

The University of Kentucky has 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 disease, bone, infectious diseases, alcoholic liver disease, the brain, and aging.

University of Medicine and Dentistry of New Jersey
Newark, NJ
PI: Gerson Weiss, M.D.

The UMDNJ–New Jersey Medical School site has a strong focus on minority and disadvantaged populations of women. Fourteen mentors offer a research experience in the areas of cardiovascular disease, diabetes, multiple sclerosis, infectious diseases, aging, 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 an M.P.H.

University of Michigan
Ann Arbor, MI
PI: Timothy R.B. Johnson, M.D.

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, with an emphasis on 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, NC
PI: Eugene Orringer, M.D.

The University of North Carolina at Chapel Hill 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, VA
PI: Mary Nettleman, M.D.

The Virginia Commonwealth University 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 the 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, MO
PI: Clay Semenkovich, M.D.

Twenty-five mentors provide an integrated focus on women's health research across eight focus areas: autoimmune disease, cardiovascular disease, complications of pregnancy, diabetes, obesity and metabolism, osteoporosis, infectious diseases, 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, CT
PI: Carolyn Mazure, M.D.

The Yale program centers on women's health and substance abuse and includes 25 mentors from a broad array of basic, clinical, and social science disciplines. Areas of emphasis include the 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 with respect to 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 I Evaluation

The ORWH, in conjunction with the NICHD, applied for and received NIH Director's Discretionary Funds to evaluate the BIRCWH I program. This program review had several purposes:

- To assess initial program outcomes;
- To enhance program management;
- To enhance program monitoring; and
- To inform BIRCWH IV RFA.

The evaluation looked at several program outcomes for scholars, including the effective mentoring of scholars; participation in interdisciplinary research and training during and after BIRCWH funding; achievement of independent scientific careers; and promotion of scientific advances in women's health research. The following metrics were examined in an informal evaluation of the BIRCWH program:

- Research independence;
- Global metric to look at amount of collaborative research generated by the BIRCWH centers;
- Assessment of scholars based on change from baseline level;
- Percentage of scholars who continue to conduct research in women's health post-BIRCWH;
- Publications: high-impact versus low-impact journals;
- Number of grants submitted per scholar compared to the number funded;
- Percentage achieving employment in academia;
- Number of scholars teaching clinical research methods;
- Number publications, positions, awards, honors, and oral presentations.

The findings of this evaluation indicate that the 12 BIRCWH I grantees successfully implemented this career development program and are leveraging additional resources for their scholars. Of the scholars who exited the program and who responded to the survey, 97 percent (n = 60) are pursuing careers in women's health research, and 85 percent are engaged in interdisciplinary research. Nearly all of the respondents, (93 percent or 57 scholars) are working in an academic institution, and 57 percent (n = 35) were in tenure-track positions. Sixty-six respondents

had submitted an NIH grant application with an overall success rate of 35 percent. Most scholars (90 percent or 50 scholars) had maintained contact with their mentors. The average public investment of $277,817 per scholar points to the need to continue to track these scholars as they pursue interdisciplinary clinical, translational, health services, and/or basic research and contribute to women's health.

BIRCWH II (2002-2006)

Several NIH ICs participated in the second solicitation for the BIRCWH program (RFA-OD-02-001), including the ORWH, NIA, NIAAA, NIAMS, NICHD, NIDCR, NIDDK, NIMH, ODS, and AHRQ. The following is a description of programs supported under the BIRCWH II program.

Boston Medical Center
Boston, MA
PI: Rebecca Silliman, M.D., Ph.D.

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 represent five major research areas: prevention research, health services outcomes and effectiveness research, addiction medicine, and issues of aging women, including the consequences of multiple caregiver roles. Scholars enter into one of two pathways: basic research for 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, RI
PI: Donald Coustan, M.D.

Brown University and its affiliated hospitals have a cross-institutional program organized around five major areas: prevention and behavior change; gender issues in women's health addressed through health services research; HIV/AIDS in women; and obstetric and gynecologic research, including perinatal diagnosis and management, screening in early pregnancy, transitional immunology, 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 who cut across institutions, including Women and Infants Hospital, the George Anderson Outcomes Measurement Unit, and the Woods Hole Marine Biological Laboratory.

Duke University
Durham, NC
PI: R. Sanders Williams

Duke University joined forces with the North Carolina Central University in designing a program to contribute to the improvement in women's health. The research program revolves around four main themes: clinical trials and outcomes; decisionmaking 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, pharmacology of the pelvic floor, and the molecular biology of nicotine addiction. More than 25 mentors who 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 toward a master's degree in health sciences or clinical research.

Magee-Women's Health Corporation
Pittsburgh, PA
PI: James Roberts, M.D.

This program is orchestrated through the Magee Women's Research Institute to provide an integrated approach to interdisciplinary research in women's health. It is 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 themes.

University of Maryland
Baltimore, MD
PI: Patricia Langenberg, M.D.

The University of Maryland program includes collaborations 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 and 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, NY
PI: John Larose, M.D.

SUNY Downstate offers a program that links SUNY Downstate Medical Center 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 span basic and clinical aspects related to women's health. Core research areas include 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 and Science University
Portland, OR
PI: Christine Cassel, M.D.

The Oregon Health and Science University (OHSU) program is based in the School of Medicine, but the program also draws on four exceptional OHSU centers, including the Center for Women's Health, the Heart Research Center, the 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 and is centered on 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, PA
PI: Jerome Strauss, M.D., Ph.D.

This program is located in the Center for Research for Reproduction and Women's Health at the University of Pennsylvania. It 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 diseases. The program offers the possibility of enrollment in a master's or doctoral program. Scholars begin with a period of mentored research training before transition into independent research with faculty appointment.

Stanford University
Stanford, CA
PI: Linda Guidice, M.D., Ph.D.

Stanford University offers mentoring in women's health research from bench to bedside and from basic to clinical research. The program features more than 23 mentors from a variety of disciplines. The major research areas of this program include midlife aging and cardiovascular disease, adolescent health, medical information technology, medicine with a focus on cardiovascular disease and diabetes, cancer, reproductive diseases and urogenital health, genetics, cancer biology, and tissue engineering. Scholars have two pathways available, basic and clinical research.

Tulane University
New Orleans, LA
PI: Paul Whelton, M.D., M.Sc.

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 experience in basic, biomedical, behavioral, and health services research. The areas of research in this program focus on two areas in women's health that warrant additional attention: cardiovascular disease and hypertension. The ultimate goal

of this program is to train scientists to address sex/gender and disparities issues in cardiovascular health research.

University of Utah
Salt Lake City, UT
PI: Eli Adashi, M.D.

The University of Utah has a program that includes collaborations with 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 and neurological disorders, and oncologic disorders. Scholars have a choice of two program levels, entry for those with limited research experience and advanced for those with significant prior research experience. Scholars also have the option of pursuing an innovative program leading to a master's of science degree.

Vanderbilt University
Nashville, TN
PI: Rose Marie Robertson, M.D.

This program includes a partnership between Vanderbilt University and the Meharry Medical College. The research program is designed around six interdisciplinary research themes: cancer and neoplasia, cardiovascular disease and diabetes, clinical pharmacology, neurosciences and behavioral health, endometrial biology and reproductive toxicology, and health services and outcomes research. Scholars have the opportunity to interact with 25 mentors from a variety of departments and schools, including the School of Medicine, the Institute for Public Policy Studies, various clinical departments, and the Departments of Preventive Medicine and Psychiatry. Research areas of 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.

BIRCWH III (2006-2010)

The third BIRCWH solicitation (RFA-OD-05-002) was funded by the ORWH with support from several NIH ICs, including the NICHD, NIAAA, NIAID, NIDA, NIDDK, NIEHS, NIMH, ODS, and AHRQ. The following is a description of programs supported under the BIRCWH III program.

Harvard University
Cambridge, MA
PI: Jill M. Goldstein, Ph.D.

The mission of this BIRCWH program is to develop the next generation of scientists and scientist-clinicians in the field of women's health. These scholars will contribute to understanding sex-specific vulnerabilities to the range of medical and psychiatric disorders that affect women. The program reflects a life span perspective to identify etiologic mechanisms during fetal development, puberty, adulthood, and aging. In addition, some research focuses on developmental periods specific to women, such as child-bearing years, perimenopause, and menopause.

University of California, Davis
Davis, CA
PI: Claire Pomeroy, M.D.

This BIRCWH program provides junior faculty with state-of-the-art interdisciplinary training, which will lead to an independent biomedical research career in areas relevant to women's health. Another objective of this program is to create an environment that nurtures non-traditional, cross-disciplinary collaborations in focused and interactive areas of research that are essential to improving the health of women. The UC Davis program focuses on four scientific areas: (1) neuroscience and neurodegenerative diseases and their disproportionate impact on females, (2) metabolic and nutrition-related syndromes and their repercussions on women, (3) cardiovascular science and its relationship to gender, and (4) life span biology and transitions, such as early development, adolescence, and menopause, that bring unique risks to females.

University of California, Los Angeles
Los Angeles, CA
PI: Gautam Chaudhuri, M.D., Ph.D.

This BIRCWH program includes a basic science approach to the diseases of women, including disciplines such as developmental biology, molecular genetics, and cell biology. It also includes clinical and translational research related to women's health in the areas of

behavioral science, cardiovascular science, AIDS, and aging and associated problems. All of the faculty mentors provide training that will allow the BIRCWH scholars to establish their own independent research programs applicable to the health problems of women.

University of California, San Francisco
San Francisco, CA
PI: Deborah G. Grady, M.D., M.P.H.

In this program, the University of California, San Francisco is collaborating with the Kaiser Permanente of Northern California Division of Research. This program provides training for scholars who are interested in women's health. The program is organized around 10 interdisciplinary research teams in the following areas: breast cancer, cardiovascular disease, complementary and alternative medicine, dementia and cognitive dysfunction, HIV in women, menopause and hormone therapy, obesity, osteoporosis and osteoarthritis, screening for disease and urinary incontinence.

University of Cincinnati
Cincinnati, OH
PI: Leslie Myatt, Ph.D.

The goal of this program is to establish an Interdisciplinary Research Careers in Women's Health Scholars Program to identify and train junior faculty members at the College of Medicine at the University of Cincinnati and Children's Hospital Medical Center in the area of women's health research. This program is based in the Department of Obstetrics and Gynecology but includes mentors from eight academic departments of the medical school. Departments participating in this program include Cell Biology, Environmental Health, Molecular and Cellular Physiology, Molecular Genetics, Pathology and Laboratory Medicine, Pharmacology and Cell Biology, and the College of Pharmacy. In addition, four divisions of the Department of Pediatrics are involved: Developmental Biology, Endocrinology, Pulmonary Biology, and Neonatology.

University of Kansas Medical Center
Kansas City, KS
PI: Patricia A. Thomas, M.D.

The long-term objective of the University of Kansas BIRCWH program is to foster the career development of junior faculty who are pursuing basic, translational, behavioral, clinical, or health services research related to women's health. Over the five-year project period, the program estimates that the number of junior faculty in tenure-track positions who are pursuing women's health research will increase by at least eight. A flexible faculty development plan tailored to meet the needs of each newly recruited faculty member is provided. Mentors have been enlisted in five areas related to women's health: women's reproductive health; maternal health; pathogenesis of diseases prevalent in women; drug design, drug delivery, and pharmacogenomics; and prevention, intervention, and health disparities.

University of Kentucky
Lexington, KY
PI: James E. Ferguson, M.D.

The primary goal of this BIRCWH program is to provide IWHR scholars with state-of-the-art interdisciplinary training in women's health research that will ensure their success in establishing independent research careers in academic medicine. To achieve this goal, the program has refined and adapted an already successful organizational structure to provide scholars with indepth training in four focused and interacting areas of women's health: (1) drug abuse and its relationship to sex and gender differences, (2) cancer as it relates to women's health, (3) hormonal regulation across a woman's life span, and (4) oral health and its impact on cardiovascular and endocrine health and pregnancy outcomes.

University of Michigan
Ann Arbor, MI
PI: Timothy R.B. Johnson, M.D.

The goal of the University of Michigan BIRCWH is to develop a cadre of new junior faculty scholars through a mentored research experience leading to independent, interdisciplinary scientific careers that address women's health concerns. Each scholar has an assigned mentor, who is an established, independent investigator with a proven track record. Mentors are selected for their commitment to teaching and history of research support. This program focuses on the following areas of

special interest: (1) pelvic floor and urogynecology research; (2) health services research; (3) reproductive science and women's medicine; and (4) biobehavioral and aging research.

University of North Carolina, Chapel Hill
Chapel Hill, NC
PI: Eugene P. Orringer, M.D.

The goal of this BIRCWH program is to select, train, and mentor junior faculty members as they transition to an independent research career. The UNC BIRCWH program is centered on three general research themes: biomarkers and therapeutics; prevention and intervention; and health issues of the mature woman. Each of these themes is relevant to women's health, well-suited to interdisciplinary collaboration, and an area of considerable strength at the university.

University of Texas Medical Branch
Galveston, TX
PI: Abbey B. Berenson, M.D.

The BIRCWH program at the University of Texas Medical Branch (UTMB) trains successful, independent investigators in women's health. The program focuses on six areas of strength in women's health research on the UTMB campus: minority health and health disparities, geriatrics, endocrinology, infectious diseases and immunology, addiction, and adolescent health. The program places special emphasis on the health needs of poor and ethnically diverse women.

Washington University
St. Louis, MO
PI: Kenneth S. Polonsky, M.D.

The long-term objective of this BIRCWH program at Washington University is to produce independent investigators to conduct interdisciplinary research in women's health. The specific aim of the program is to identify outstanding young scientists committed to women's health who have completed fellowship training, match them with mentors working in an environment that promotes interdisciplinary research, and provide them with career development experiences leading to their independence. By bridging fellowship training and independent faculty status, this BIRCWH program has the potential to significantly impact women's health by increasing the number of outstanding scientists. Disease areas of interest in this program include depression, osteoporosis, lupus, type 2 diabetes, urinary tract infections, heart attacks, certain cancers, and infertility.

BIRCWH Research Topics

The BIRCWH program has been in operation since 2000 and continues with funding in 2005 and 2006 under BIRCWH II and BIRCWH III. The following is a list of selected topics that have been addressed by BIRCWH scholars.

Mental Health

- Assessing the impact of SSRI antidepressants on women's depressive illness;
- Sexual harassment and psychological health of women;
- Emergency department screening and intervention to improve the safety and health of battered women;
- Examining communication and power dynamics of female patients and their health care providers; and
- 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 and the relationship to gender, ethnicity, diabetes treatment regimen; and
- Mechanism by which diabetes contributes to cardiovascular disease (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 of CVD associated with mental health risk factors;
- Modifiable environmental risk factors and genetic risk determinants for CVD and chronic kidney disease;
- Properties of a single item global health measure for predicting patient outcomes and high-risk CVD; and
- Vascular disease in women.

Arthritis and Musculoskeletal Health

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

Neurological Disorders

- Gender susceptibility to neurological dysfunctions associated with altering GABA receptor signaling;
- Effect of gender and phenotype on neurotransmitter efficiency-related disorders; and
- Hormone changes induced by seizure activity in rats.

Menopausal Hormone Therapy

- Estrogen and angiogenesis;
- Effects of estrogen on cardiac fibrosis after myocardial infarction; and
- Hormone therapy and effects on cognition.

Sex/Gender

- Sex differences in substance abuse;
- Importance of gender and social supports in the nursing home setting; and
- 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; and
- Smoking cessation rates for women with abnormal PAP smears.

Reproductive Health

- Risk factors for sexually transmitted infections among women in an Alabama HIV clinic;
- Increased vaginal levels of a collagen synthesis marker 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 a mathematical model;
- NK cell gene expression in normal pregnancy vs. recurrent spontaneous miscarriage;
- Insulin sensitivity and pregnancy-related weight gain;
- Estrogen and prolactin in septic shock; and
- 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;

- Immunogenic vs. non-immunogenic profiles in ovarian cancer;
- Causes and consequences of genetic instability in ovarian cancer;
- Mechanisms of ischemia, reperfusion injury, and ischemic preconditioning in breast cancer; and
- Universal breast cancer antigens as targets linking early detection and therapeutic vaccination.

Molecular Biology/Genetics

- Genetics of endometriosis using microarrays; and
- Genetics of breast cancer.

Health Services/Health 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; and
- Social and cultural factors in managing chronic diseases in Caribbean immigrants.

Specialized Centers of Research (SCORs) on Sex and Gender Factors Affecting Women's Health (2002-2006)

The ORWH and co-sponsors seek to promote interdisciplinary research in sex/gender factors through Specialized Centers of Interdisciplinary Research (SCOR). Funding for the centers totals approximately $11 million per year for five years, with co-funding provided by the NIAMS, NICHD, NIDDK, NIDA, NIMH, NIEHS, and the FDA. Each SCOR promotes interdisciplinary collaborations and develops a research agenda bridging basic and clinical research on sex/gender factors underlying a priority issues in women's health. The SCOR program complements other federally supported programs addressing women's health, including the BIRCWH program and the Women's Reproductive Health Research Career Development Centers (WRHR), as well as research grants solicited through numerous NIH RFAs and PAs.

The ORWH funded 11 SCORs in FY 2002. These centers provide new opportunities for interdisciplinary approaches to studies on how sex and gender factors affect women's health. Each SCOR promotes interdisciplinary collaborations and the development of a research agenda that bridges basic and clinical research on sex and gender factors that address priority women's health issues. Research priority areas addressed by the SCORs include mental health, reproductive health, pain disorders, and urinary tract health. The following describes SCOR themes, center directors, individual projects, and affiliations.

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

Models are being 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
PI: Kathleen Brady, M.D., Ph.D.

The role of sex and gender differences in substance abuse relapse are being studied, with particular emphasis on elucidating factors contributing to relapse. The substances included in this SCOR's research are tobacco, cocaine, and alcohol.

Northwestern University
Genes, Androgens, and Intrauterine Environment in Polycystic Ovarian Syndrome
PI: 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
PI: Emeran Mayer, M.D.

Sex and gender factors underlying the pathophysiology of irritable bowel syndrome and interstitial cystitis are being evaluated.

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

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

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

This SCOR is focusing on neuronal mechanisms underlying sex differences in pain sensitivity, with particular attention to visceral and temporomandibular pain.

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

Studies at this SCOR focus on 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
PI: Gerald Schatten, Ph.D.

This SCOR is studying genetic and environmental factors that contribute to adverse pregnancy outcomes, particularly recurrent pregnancy loss.

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

Investigators at this SCOR are studying the mechanisms by which drugs are transported in the body, with a special emphasis on maternal and fetal drug exposure during pregnancy. Investigators are looking at alterations in drug transport that occur during pregnancy.

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

This SCOR is studying the molecular basis of acute and recurrent urinary tract infections (UTIs) in women. They are also looking at the epidemiology of UTIs, which are among the most common infections in the U.S. and primarily affect women.

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

Sex, stress, and cocaine addiction form the research core of this interdisciplinary program. It is hoped that findings will lead to sex-specific prevention strategies and treatments for cocaine addiction.

SCOR Evaluation

The ORWH established an External Advisory Committee (EAC) to review the SCOR program and to provide guidance to the Office. Members of the CCRWH and ACRWH were selected to serve on this review. The nine-member committee noted that the SCORs had begun to demonstrate success in meeting their scientific objectives. They had proven successful in mobilizing scientists of diverse disciplines and bringing their expertise to bear on the examination of how sex and gender factors contribute to health and disease. Significant progress also was demonstrated in each center regarding the development of experimental methodology, implementation and expansion of research, and recruitment of clinical participants. SCOR investigators are actively promoting sex and gender research through pilot projects, seminars, and training of junior investigators. These investigators have also taken the initiative to embark on collaborations with other SCORs.

Interdisciplinary Symposia

In FY 2005 and 2006, the ORWH held the second and third annual Interdisciplinary Symposia on Research on Women's Health. These symposia brought together principal investigators and scholars from the BIRCWH I, II, and III and the SCOR programs. The meeting objectives included increasing knowledge on women's health from collaborative and interdisciplinary research activities; understanding sex and gender differences that contribute to biological differences in cellular, tissue, and organ responses between men and women or conditions that have enhanced clinical presentation in women; and understanding the effects of gender on psychological, social, and behavioral determinants of health and disease.

In conjunction with the interdisciplinary symposium, the ORWH developed a program with The George Washington University School of Public Health and Public Policy called *The Federal Legislative Process and Women's Health Policy: An Introduction for NIH Researchers*. This daylong meeting, which was held in 2006, included both presentations and a poster session. The purpose of the meeting was to introduce scientists specializing in women's health research to the federal legislative process. The program featured leading experts in women's health policy and the legislative process with respect to the creation and funding of health programs, legislative issues in women's health policies, and concepts and devices to emphasize women's health issues to members of Congress. Following a general overview in the morning, two major afternoon roundtables were devoted to a discussion of the NIH reauthorization process as well as other major developments in federal legislation and women's health policy.

Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

Historical Perspective

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the 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, the 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 the NIH recognized the need to address the inclusion of minority populations. As a result, a later 1987 version of the NIH guide, a policy ***encouraging*** the inclusion of minorities in clinical studies was first published.

To ensure that the policies for inclusion were firmly implemented by the NIH, the Congress made what had previously been policy into Public Law, through a section in the NIH Revitalization Act of 1993 (PL 103 43)[7], titled *Women and Minorities as Subjects in Clinical Research*. In 1994, the 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 the 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;

[7] Public Law 103-43, 107, Stat. 22 (codified at 42 U.S.C. 189.a-1) [Sec. 486(187d)(d)].

- that cost is not allowed as an acceptable reason for excluding these groups; and
- that the 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*[8] in March 1994, and they became effective in September 1994. The result was that the NIH could not and would not fund any grant, cooperative agreement, or contract or support any intramural project to be conducted or funded in FY 1995 and thereafter that did not comply with this policy. Strategies to ensure uniform implementation of the revised guidelines across the NIH were developed through the establishment and deliberations of an NIH Tracking and Inclusion Committee made up of representatives of the directors of each of the NIH ICs. This trans-NIH committee, convened by the 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 (OER), the Office of Intramural Research (OIR), and other components of the NIH, the ORWH coordinates the activities to develop and establish 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, the NIH conducted extensive training. In June 1994, the ORWH convened a meeting of Institutional Review Board (IRB) chairs to discuss their role in implementing the revised policy. Training was especially important in light of 1990 GAO findings that an earlier policy was inconsistently applied and had not been well communicated or understood within the 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 requirements.

Continuing Implementation and Monitoring Activities

Following a congressional request for an assessment of the NIH's progress in implementing the1994 guidelines on the inclusion of women in clinical research, the GAO issued another report in May, 2000, titled *Women's Health: NIH Has Increased Its Efforts to Include Women in Research.*[9] It concluded that in the past decade, the NIH has made significant progress in implementing a strengthened policy on including women in clinical research.

The GAO report also included two specific recommendations to the Director of the 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, the ORWH, the OER, and the OIR, to reexamine the NIH's system for tracking data on the inclusion of women and minorities in clinical research, to recommend any necessary changes to improve its accuracy and performance, and to 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. Significant actions in 2001 included:

[8] NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508-14513 (1994).

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

- Updating the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research and posting it on the ORWH home page at http://orwh.od.nih.gov/inclusion.html, and NIH Web page, *Inclusion of Women and Minorities Policy Implementation* at: http://grants.nih.gov/grants/funding/women_min/women_min.htm.;

- Developing a new term and condition of award statement for awards made after October 1, 2000 that have NIH-defined Phase III clinical trials;

- Incorporating language in the NIH solicitations for grant applications and contract proposals to clarify the submission requirement for NIH-defined Phase III clinical trials, a description of plans for sex/gender and/or race/ethnicity analysis including subgroups, if applicable, and reporting accrual annually and results of analyses, as appropriate; and

- Developing guidelines and instructions for reviewers and Scientific Review Administrators (SRAs) 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 and developing instructions for the proper documentation to include in summary statements to address adherence to these policies.

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 initiatives were implemented for review, grants management, and program staff, including specific topics addressing revisions to the NIH inclusion policy, a grants policy updates, and Scientific Review Administrator (SRA) orientation on specific issues related to review meetings and proceedings.

The PHS 398 Grant Application was significantly revised to provide additional instructions about the women and minorities inclusion policy and became mandatory as of May 10, 2005. The PHS 398 instructions have also been included in the new federal application form SF-424 for NIH grants using the federal Grants.gov system (see http://era.nih.gov/ElectronicReceipt/). The application instructions include two significant changes in definitions. First, the NIH required use of a revised definition of clinical research based on the 1997 Report of the NIH Director's Panel on Clinical Research and adopted by the NIH. Second, the Office of Management and Budget (OMB) Directive 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting, revised the racial and ethnic categories to be used when reporting population data (see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html). In addition, the revised NIH policy reemphasized that NIH-defined Phase III clinical trials must be designed and conducted in a manner to allow for a valid analysis of whether the variables being studied affect women or members of minority groups differently from other subjects.

Many of the training sessions are available electronically for all NIH staff, and the OER has made available existing training materials on the internal population tracking system Web site. 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. (See Appendix E for a list of NIH Tracking and Inclusion Committee members.)

Communication and Outreach Efforts to the Scientific Community

NIH staff provides outreach to the scientific community to help increase understanding of the revised inclusion policy and OMB requirements. These training and outreach efforts are designed to improve understanding of the NIH inclusion policy and to assist investigators and NIH staff in appropriately addressing these issues throughout the research grant and contract process. Investigators are instructed to address women and minority inclusion issues in the development of their applications and proposals for clinical research.

Reference documents, such as the *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clini-*

cal Research (http://orwh.od.nih.gov/inclusion/outreach.pdf) and the *Frequently Asked Questions (FAQs) for the Inclusion, Recruitment, and Retention of Women and Minority Subjects in Clinical Research* (http://orwh.od.nih.gov/inclusion/outreachFAQ.pdf) have been published and distributed for investigators and NIH staff. These publications discuss the elements of recruitment and retention, the current NIH inclusion policy, the 1997 OMB requirements for reporting race and ethnicity data, as well as information for application submission, peer review, and funding. Both documents are posted on the ORWH Web site http://orwh.od.nih.gov as well as on the NIH Web site for the inclusion of women and minorities policy implementation at http://grants1.nih.gov/grants/funding/women_min/women_min.htm. The revised Outreach Notebook and FAQs continue to be available to the research community to further explore the inclusion policy and its intent. In addition, a slide show titled *Sex/Gender and Minority Inclusion in NIH Clinical Research: What Investigators Need to Know!* is available electronically and in hard copy for NIH staff use in working with the extramural community.

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 U.S. The number of women or minority subpopulations included in a particular study depends upon the scientific question that the study is seeking to address and the prevalence of the disease, disorder, or condition under investigation among women and minority subpopulations.

Scientific Review Groups (SRGs) are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study. The SRG determines that the implementation plan for an application is 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 cannot be funded until NIH staff is assured that revised inclusion plans from the investigators comply with the NIH inclusion policy requirements. 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.

The NIH has monitored aggregate demographic data for study populations utilizing an NIH computerized tracking system since FY 1994, and tracking the inclusion of women and minorities in clinical studies is well established in all ICs. Members of the NIH Tracking and Inclusion Committee continuously 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, the 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 of investigator data reporting for NIH staff. An eRA Population Tracking User Group consisting of representatives from several ICs provides continuous feedback related to system use.

The reporting of aggregate extramural and intramural data enables the NIH to measure and monitor inclusion, to formulate more specific questions about gaps in enrollment, and to better design studies to respond to those questions. Since the launch of the new tracking system in 2002, the NIH has improved monitoring for IC and investigator compliance with the NIH inclusion policy. Additionally, longitudinal examinations of trends for human subject research participation are underway, and reports are now generated on foreign and domestic participation. However, racial and ethnic trend reporting will be more difficult because of a

change in how data are collected and reported (OMB Directive 15, 1997).

A review of intramural inclusion data indicates that the intramural research program continues to be 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. The MEC designed and endorsed the standards for clinical research within the NIH Intramural Research Program (IRP), which set forth guidelines for the infrastructure, training, education, and monitoring required for safe and effective conduct of clinical research.

Format Changes for Reporting Race and Ethnicity Data

Beginning in FY 2002, the NIH changed how data are collected and reported based on the 1997 OMB Directive 15 minimum standards for maintaining, collecting, and 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; the 1977 OMB standards used a combined race and ethnicity format. The NIH aggregate population data tables describe data using both the 1997 and 1977 OMB standards for reporting data on race and ethnicity. Since 2002, the number of studies reporting data using the 1997 format (NEW FORM) has steadily increased, while the number of studies using the 1977 format (OLD FORM) has steadily decreased, as the studies funded before FY 2002 are completed.

The 1997 OMB reporting format (NEW FORM) and standards do not allow direct comparison of ethnic and racial data with similar data collected under the 1977 OMB reporting format (OLD FORM) and standards because the categories and methods for collecting the data are fundamentally different. Changes in the standardization of definitions and business rules across the NIH for improving the data entered in the population tracking system are reflected in data reported beginning in FY 2002. While implementation of these changes will improve the consistency and comparability for future reporting, comparisons with data prior to FY 2002 are difficult.

As demonstrated by the following, the primary differences are: (1) the Hispanic population is considered an ethnic category 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. Race and ethnicity data from the OLD and NEW FORMs are combined differently, as described in the following, for purposes of reporting on the minority population enrolled in NIH clinical research:

- The OLD FORM uses the 1977 OMB combined Race and Ethnicity Format, which has mutually exclusive categories and allows Hispanics to be reported as either "Hispanic, Not White" or "White."

- The NEW FORM uses the 1997 OMB Race and Ethnicity Categories, with separate reporting for Ethnicity (Hispanic or Latino; Not Hispanic or Latino) and race (Part A). In this format, an individual is classified both by Ethnic Category and by Race Category. Part B of the NEW FORM, therefore, provides a distribution of only "Hispanics or Latinos" by the five main race categories. Since minority categories are defined to include both "Hispanic or Latino ethnicity" and non-white racial categories when providing summary totals of minorities, it is necessary to add "White Hispanics" and "Unknown/Other Hispanics" based on their ethnicity to the non-white racial categories.

- Hispanics are defined by country of origin and may be identified as belonging to any one or more than one race category.

TABLE 4

OLD FORM (1977) vs. NEW FORM (1997)

Race/Ethnicity Category	*Minority Total OLD FORM*	*Minority Total NEW FORM*
OLD FORM: Combined 1977 OMB Race/Ethnicity Categories		
American Indian/Alaska Native	●	
Asian/Pacific Islander	●	
Black or African American	●	
Hispanic, Not White	●	
White		
Unknown/Other		

NEW FORM: Separate 1997 OMB Race/Ethnicity Categories		
Part A: Total Enrollment Report		
Ethnic Category		
Hispanic or Latino†		
Not Hispanic or Latino		
Unknown (ethnicity not reported)		
Ethnic Category Total of All Subjects*		
Racial Categories		
American Indian/Alaska Native		●
Asian		●
Black or African American		●
Hawaiian/Pacific Islander		●
White		
More Than One Race		●
Unknown/Other		
Racial Categories: Total of All Subjects*		
Part B: Hispanic Enrollment by Race		
American Indian/Alaska Native		
Asian		
Black or African American		
Hawaiian/Pacific Islander		
White (Hispanic)		●
More Than One Race		
Unknown/Other (Hispanic)		●
Racial Categories: Total of Hispanics or Latinos†		

* The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

† The "Hispanic or Latino"(Part A) must be equal to "Racial Categories: Total of Hispanics or Latinos"(Part B).

Definitions

Clinical Research as Defined by the 1997 Report of the NIH Director's Panel on Clinical Research

Clinical research comprises three types of studies: (1) patient-oriented research; (2) epidemiologic and behavioral studies; and (3) outcomes research and health services research. Patient-oriented research refers to 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.

NIH-Defined Phase III Clinical Study

For the purpose of these guidelines, an NIH-defined "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 control 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. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Valid Analysis

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process, such as randomization;
- unbiased evaluation of the outcome(s) of study participants; and
- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

Significant Difference

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant but clinically small difference that is of very little clinical importance. Conversely, with less information, one could find a large difference of potential importance that is not statistically significant.

Domestic Organization

A public (including a state or other governmental agency) or private non-profit or for-profit organization, which is located in the U.S. or its territories, is subject to U.S. laws and assumes legal and financial accountability for awarded funds and for the performance of the grant-supported activities.

Foreign Institution

An organization located in a country other than the U.S. and its territories that is subject to the laws of that country, regardless of the citizenship of the proposed principal investigator (PI).

Summary Report of NIH Inclusion Data

NIH Aggregate Population Data Reported in FY 2005 and 2006

Data on inclusion are tabulated from human subject populations in NIH-defined Phase III clinical trials and other human subject research studies. NIH clinical research studies are determined in accordance with the NIH definition of clinical research (see definitions above) to include, for example, non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, and database studies. Analysis of aggregate NIH data on inclusion for FY 2005 and 2006 document that substantial numbers of women and men, especially non-minority men, and minorities have been included as research subjects in NIH-defined Phase III clinical trials and other human subject research studies during these fiscal years. Because the data included in the tables are aggregate data from across the NIH, they do provide documentation of tracking and inclusion across the NIH and some degree of analysis of the data. But caution should be utilized to not over-interpret the figures that are provided. The NIH Tracking and Inclusion Committee has provided below conclusions that can be reasonably drawn from the data.

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 Web site at http://orwh.od.nih.gov/inclusion.html. For this biennial report on women's health, the data and their description presented in the following come from *Comprehensive Reports: Tracking of Human Subjects Research as Reported in Fiscal Year 2005 and Fiscal Year 2006*[10] as well as the comprehensive report for FY 2004 and FY 2005.[11] Both reports are available online at http://orwh.od.nih.gov/inclusion.html. Several tables from the FY 2005 and 2006 report have been included below to illustrate the type of data collected and reported by the NIH on inclusion of women and minorities. For this biennial report, some tables may vary slightly or be formatted slightly differently from those presented in the comprehensive reports to clarify reporting here. The reader is referred to the original comprehensive reports for more detailed tables and discussion of the data.

NIH Clinical Research: FY 2005 and 2006

In FY 2005, there were 14,798 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,233 protocols reported human subject participation. Of these, 96.4 percent were domestic protocols, and 3.6 percent were foreign protocols. Approximately 15.7 million participants were enrolled in extramural and intramural research protocols of which 80.6 percent were domestic participants and 19.4 percent were foreign participants. Of the 15.7 million participants, 60.4 percent were women, 37.8 percent were men, and 1.8 percent did not provide sex identification. Further, 39.7 percent of the total participants and 27.4 percent of the domestic-only participants were reported as minorities following the OMB categories for race and ethnicity. (See Table 10 and Table 6 of the FY 2005 and 2006 Comprehensive Report.)

Correspondingly, in FY 2006 there were 15,320 extramural and intramural clinical research protocols, including Phase III and other clinical studies, of which 10,758 protocols reported human subject participation. Of these, 95.7 percent were domestic protocols, and 4.3 percent were foreign protocols. Approximately 14.8 million participants were enrolled in extramural and intramural research protocols of which 77.0 percent were domestic participants and 23.0 percent were foreign participants. Of the 14.8 million participants, 63.9 percent were women, 34.9 percent were men, and 1.3 percent did not provide sex identification. Further, 43.1 percent of the total participants and 28.9 percent of the domestic-only participants were reported as minorities following the OMB categories for race and ethnicity. (See Table 5 below or Table 1 of the FY 2005 and 2006 Comprehensive Report.)

Although the number of participants in all extramural and intramural clinical research decreased (15.7 million in FY 2005 and 14.8 million in FY 2006), there was no significant

[10] Pinn, Vivian W., Roth, Carl, Bates, Angela C., Caban, Carlos E., and Jarema, Kim. Comprehensive Report: Tracking of Human Subjects Research as Reported in Fiscal Year 2005 and Fiscal Year 2006. Department of Health and Human Services/National Institutes of Health, April 2007.

[11] Pinn, Vivian W., Roth, Carl, Bates, Angela C., Caban, Carlos E., and Jarema, Kim. Comprehensive Report: Tracking of Human Subjects Research as Reported in Fiscal Year 2004 and Fiscal Year 2005. Department of Health and Human Services/National Institutes of Health, 2006.

change in the ratio of women and men (60.4 percent females and 37.8 percent males in FY 2005; 63.9 percent females and 34.9 percent males in FY 2006). One large study involving approximately 1.6 million participants that ended in FY 2005 and, therefore, was not included in the FY 2005 figures, accounted for the net decreased number of participants reported.

NIH-Defined Phase III Clinical Research: FY 2005 and 2006

In FY 2005, there were 665 extramural and intramural Phase III clinical research protocols, of which 547 protocols reported human subject participation. Of these, 94.5 percent were domestic protocols, and 5.5 percent were foreign protocols. Approximately 493,000 participants were enrolled in extramural and intramural Phase III research protocols, of which 88.8 percent were domestic participants and 11.2 percent were foreign participants. Of the 493,000 participants, 59 percent were women, 40 percent were men, and 1 percent did not provide sex identification. Further, 31.3 percent of the total participants and 25.1 percent of the domestic-only participants in Phase III clinical research were reported as minorities following the 1997 OMB categories for race and ethnicity. (See Table 11 and Table 7 of the FY 2005 and 2006 Comprehensive Report.)

According to the trend summaries in this report, of the 210 extramural and intramural Phase III research protocols that report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 12.5 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 6.9 percent, Asian/Pacific Islanders were 5.6 percent, and Whites (not Hispanic) 73.2 percent of the participants. The categories, Hawaiian/Pacific Islander and More Than One Race, were not designations with the 1977 OMB standards. (See Table 11 and Table 7 of the FY 2005 and 2006 Comprehensive Report.)

Furthermore, in FY 2005, there were 337 extramural and intramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 28.5 percent and lowest for Hawaiian/Pacific Islanders 0.3 percent. Asians represented 5.2 percent, American Indian/Alaska Natives 1.2 percent, and Whites 57.3 percent of participants. Participants identifying as More Than One Race were 1.7 percent of the total number of participants. In addition, 5.8 percent did not identify a race category. Of the 337 extramural and intramural Phase III research protocols designating an ethnicity in FY 2005, 88.6 percent of total participants identified as "Not Hispanic," 5.9 percent of the total participants identified as "Hispanic or Latino," and 5.5 percent of the total participants did not identify an ethnicity category. The racial distribution of the "Hispanic or Latino" participants is also provided separately. (See Table 11 and Table 7 of the FY 2005 and 2006 Comprehensive Report.)

Correspondingly, in FY 2006 there were 760 extramural and intramural Phase III clinical research protocols, of which 624 protocols reported human subject participation. Of these, 90.4 percent were domestic protocols, and 9.6 percent were foreign protocols. Approximately 499,430 participants were enrolled in extramural and intramural Phase III research protocols, of which 80.2 percent were domestic participants and 19.8 percent were foreign participants. Of the 499,430 participants, 62.9 percent were women, 36.0 percent were men, and 1.1 percent did not provide sex identification. Further, 33.5 percent of the total participants and 20.7 percent of domestic-only participants in Phase III clinical research were reported as minorities following the OMB categories for race and ethnicity. (See Table 7 or Table 3 of the FY 2005 and 2006 Comprehensive Report.)

According to the trend summaries, of the 215 extramural and intramural Phase III research protocols that report following the 1977 OMB standards in FY 2006, minority representation was highest for Blacks (not Hispanic) at 8.9 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 4.1 percent, Asian/Pacific Islanders were 7.3 percent, and Whites (not Hispanic) 76.5 percent of the participants. The categories,

Hawaiian/Pacific Islander and More Than One Race, were not designations with the 1977 OMB standards. (See Table 11 and Table 7 of the FY 2005 and 2006 Comprehensive Report.)

Moreover, in FY 2006, there were 409 extramural and intramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting by both race and ethnicity. Accordingly, minority representation by race was highest for Blacks at 18.8 percent and lowest for Hawaiian/Pacific Islanders 0.2 percent. Asians represented 12.0 percent, American Indian/Alaska Natives 1.7 percent, and Whites 47.0 percent of participants. Participants identifying as More Than One Race were 1.6 percent of the total number of participants. In addition, 18.7 percent did not identify a race category. Of the 409 extramural and intramural Phase III research protocols designating an ethnicity in FY 2006, 75.0 percent of total participants identified as "Not Hispanic," 11.5 percent of the total participants identified as "Hispanic or Latino," and 13.5 percent of the total participants did not identify an ethnicity category. (See Table 11 and Table 7 of the FY 2005 and 2006 Comprehensive Report.) Although the number of participants in Phase III extramural and intramural clinical research slightly increased (493,000 in FY 2005 and 499,430 in FY 2006), there was no significant change in the ratio of women and men (59.0 percent females and 40.0 percent males in FY 2005; and 62.9 percent females and 36.0 percent males in FY 2006).

The following sections provide data on extramural research and intramural research separately.

Extramural Clinical Research FY 2005 and 2006

In FY 2005, there were 13,003 extramural clinical research protocols, including Phase III and other clinical studies, of which 8,763 protocols reported human subject participation. Approximately 13.8 million participants were enrolled in extramural research protocols, of which 62.1 percent were women, 36.0 percent were men, and 1.9 percent did not provide sex identification.) (See Table 2 and Appendix Table 3A of the FY 2004 and 2005 Comprehensive Report.)

Correspondingly, in FY 2006, there were 13,522 extramural clinical research protocols, including Phase III and other clinical studies, of which 9,235 protocols reported human subject participation. Of these, 95.7 percent were domestic protocols, and 4.3 percent were foreign protocols. Approximately 13.02 million participants were enrolled in extramural research protocols, of which 76.6 percent of the total enrollment is domestic participants and 23.4 percent of the total enrollment is foreign participants. Of the 13.02 million participants, 65 percent were women, 33.8 percent were men, and 1.2 percent did not provide sex identification. Further, 45.9 percent of the total participants were reported as minorities following the OMB categories for race and ethnicity. (See Table 6 and Table 2 and Appendix Table 3A of the FY 2005 and 2006 Comprehensive Report.)

Although the number of participants in all extramural clinical research decreased (13.8 million in FY 2005 and 13.02 million in FY 2006), there was no significant change in the ratio of women to men (62 percent females and 36 percent males in FY 2005 and 65 percent females and 34 percent males in FY 2006). However, in FY 2006, when sex-specific studies were excluded, the proportion of women and men in all extramural clinical research was proportional to the percentages of the general population (52.4 percent females and 45.8 percent males).

NIH-Defined Phase III Extramural Clinical Research FY 2005 and 2006

In FY 2005, there were 621 extramural Phase III clinical research protocols, of which 511 protocols reported human subject participation. Of these, 88.5 percent were domestic protocols, and 4.9 percent were foreign protocols. Approximately 465,956 participants were enrolled in extramural Phase III research protocols, of which 86 percent of total enrollment is domestic participants and 8.6 percent of total enrollment is foreign participants. Of the 465,956 participants, 59.5 percent were women, 39.5 percent were men, and 1 percent did not provide sex identification. Further, 29.9 percent of the total participants in Phase III clinical research were reported as minori-

ties following the OMB categories for race and ethnicity. (See Table 4 and Appendix Table 5A of the FY 2004 and 2005 Comprehensive Report.)

In FY 2006, there were 707 extramural Phase III clinical research protocols, of which 580 protocols reported human subject participation. Approximately 467,954 participants were enrolled in extramural Phase III research protocols, of which 63.5 percent were women, 35.4 percent were men, and 1 percent did not provide sex identification. (See Table 8 and Table 4 and Appendix Table 5A in the FY 2005 and 2006 Comprehensive Report.)

Correspondingly, in FY 2006, there were 382 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 19.7 percent and lowest for Hawaiian/Pacific Islanders at 0.2 percent. Asians represented 12.67 percent, American Indian/Alaska Natives 1.8 percent, and Whites 46.32 percent of participants. Participants identifying as More Than One Race were 1.5 percent of the total number of participants. In addition, 17.8 percent did not identify a race category. Of the 382 extramural Phase III research protocols designating an ethnicity in FY 2006, 75.8 percent of total participants identified as "Not Hispanic," 11.14 percent of the total participants identified as "Hispanic or Latino," and 13.1 percent of the total participants did not identify an ethnicity category. (See Appendix Table 5A of the FY 2005 and 2006 Comprehensive Report.)

In FY 2005, there were 319 extramural Phase III research protocols reporting data following the current 1997 OMB standards for reporting race and ethnicity. Minority representation by race was highest for Blacks at 30.0 percent and lowest for Hawaiian/Pacific Islanders 0.28 percent. Asians represented 5.44 percent, American Indian/Alaska Natives 1.3 percent, and Whites 55.75 percent of participants. Participants identifying as More Than One Race were 1.56 percent of the total number of participants. In addition, 5.66 percent did not identify a race category. Of the 319 extramural Phase III research protocols designating an ethnicity in FY 2005, 88.7 percent of total participants identified as "Not Hispanic," 5.98 percent of the total participants identified as "Hispanic or Latino," and 5.32 percent of the total participants did not identify an ethnicity category. (See Appendix Table 5A of the FY 2004 and 2005 Comprehensive Report.)

Of the 192 extramural Phase III research protocols that report following the 1977 OMB standards, minority representation was highest for Blacks (not Hispanic) at 13.03 percent and lowest for American Indian/Alaska Natives at 0.4 percent. Hispanics represented approximately 7.23 percent, Asian/Pacific Islanders 1.81 percent, and Whites (not Hispanic) 76.1 percent of the participants. The categories, Hawaiian/Pacific Islander and More Than One Race, were not designations in the 1977 OMB standards. (See FY 2004 and 2005 Comprehensive Report.)

Although the number of participants in Phase III extramural clinical research protocols slightly increased, there was also some change in the ratio of women to men (59.5 percent female and 39.5 percent male in FY 2005 and 63.5 percent female and 35.4 percent male in FY 2006).

Intramural Clinical Research FY 2005 and 2006

Substantial numbers of women and minorities were included in NIH intramural studies in FY 2005 and 2006. In FY 2005, there were 1,795 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,470 protocols reported human subject participation. Of these, 13.7 percent of the total protocols were domestic protocols, and 0.7 percent of the total protocols were foreign protocols. Approximately 1.94 million participants were enrolled in intramural research protocols, of which 10.4 percent of the total enrollment is domestic participation and 1.9 percent of the total enrollment is foreign participation. Of the 1.94 million participants, 48.7 percent were women, 50.5 percent were men, and 0.79 percent did not provide sex identification. (See FY 2004 and 2005 Comprehensive Report.)

In FY 2005, approximately 1.94 million participants were reported in all intramural research, including Phase III clinical trials and other clinical studies. Of the 733 intramural

research protocols that report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 17.8 percent and lowest for American Indian/Alaska Natives at 1.8 percent. Blacks (not Hispanic) represented 7.5 percent, Hispanics 4.7 percent, and Whites (not Hispanic) 60.9 percent of the intramural research study population. The categories, Hawaiian/Pacific Islander and More Than One Race, were not designations in the 1977 OMB standards. (See FY 2004 and 2005 Comprehensive Report.)

For the 737 intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2005, the largest racial minority group was Blacks at 4.74 percent, and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.19 percent. Asians represented 3.1 percent, American Indian/Alaska Natives 0.42 percent, and Whites 86.2 percent of participants in all intramural clinical research. Approximately 1 percent of participants reported More Than One Race as their racial category. In addition, 4.42 percent did not identify a race category. Of the 737 intramural research protocols following the current 1997 OMB standards designating an ethnicity in FY 2005, 95.58 percent of total participants identified as "Not Hispanic," 2.10 percent of the total participants identified as "Hispanic or Latino," and 2.32 percent of the total participants did not identify an ethnicity category. (See FY 2004 and 2005 Comprehensive Report.)

Correspondingly, in FY 2006, there were 1,798 intramural clinical research protocols, including Phase III and other clinical studies, of which 1,523 protocols reported human subject participation. Approximately 1.8 million participants were enrolled in intramural research protocols, of which 55.4 percent were women, 43.0 percent were men, and 1.6 percent did not provide sex identification. (See Table 6 and Table 2 and Appendix Table 7A of the FY 2005 and 2006 Comprehensive Report.)

In FY 2006, approximately 1.8 million participants were reported in all intramural research, including Phase III clinical trials and other clinical studies. Of the 590 intramural research protocols that report data following the 1977 OMB standards, minority representation was highest for Asian/Pacific Islanders at 19.9 percent and lowest for American Indian/Alaska Natives at 3.3 percent. Blacks (not Hispanic) represented 7.2 percent, Hispanics 3.5 percent, and Whites (not Hispanic) 62.0 percent of the intramural research study population. The categories, Hawaiian/Pacific Islander and More Than One Race, were not designations in the 1977 OMB standards. (See Appendix Table 7A in the FY 2005 and 2006 Comprehensive Report.)

For 933 intramural clinical research studies that reported data following the current 1997 OMB standards in FY 2006, the largest racial minority group was Asian at 8.6 percent, and the smallest racial minority group was Hawaiian/Pacific Islanders at 0.07 percent. Blacks represented 5.0 percent, American Indian/Alaska Natives 0.4 percent, and Whites 79.1 percent of participants in all intramural clinical research. Approximately 0.8 percent of participants reported More Than One Race as their racial category. In addition, 6.0 percent did not identify a race category. Of the 933 intramural research protocols following the current 1997 OMB standards designating an ethnicity in FY 2006, 91.3 percent of total participants identified as "Not Hispanic," 4.1 percent of the total participants identified as "Hispanic or Latino," and 4.6 percent of the total participants did not identify an ethnicity category. (See Table 11A and Table 7A of the FY 2005 and 2006 Comprehensive Report.)

There was an increase in women from 48.7 percent to 55.4 percent and a corresponding decrease in men from 50.5 percent to 43.0 percent. The number of participants in all intramural clinical research decreased slightly from 1.9 million to 1.8 million from FY 2005 to 2006.

NIH-Defined Phase III Intramural Clinical Research FY 2005 and 2006

In FY 2005, there were 44 intramural Phase III clinical research protocols, of which 36 protocols reported human subject participation. Of these, 6 percent of the total protocols are domestic protocols, and 0.5 percent of the total protocols are foreign protocols. Approximately 27,044 participants were enrolled in intramural Phase III research protocols, of which 2.86 percent of total enrollment is domestic participation and 2.6 percent of total enrollment is foreign participation. Of

the 27,044 participants, 50.5 percent were women, 49.5 percent were men, and 0 percent did not provide sex identification. Further, 54.5 percent of the total participants in Phase III clinical research were reported as minorities following the OMB categories for race and ethnicity. (See Table 8 and Table 4 and Appendix Table 9A of the FY 2004 and 2005 Comprehensive Report.)

Correspondingly, in FY 2006, there were 53 intramural Phase III clinical research protocols, of which 44 protocols reported human subject participation. Of these, 6.3 percent of the total number of protocols are domestic, and 0.7 percent are foreign. Approximately 31,476 participants were enrolled in intramural Phase III research protocols, of which 54.0 percent were women, 46.0 percent were men, and 0 percent did not provide sex identification. Further, 54 percent of total participants in Phase III clinical research protocols were reported as minorities following the OMB categories for race and ethnicity. (See Table 8 and Table 4 and Appendix Table 9A of the FY 2005 and 2006 Comprehensive Report.)

There was a small increase in women (50.5 percent to 54.0 percent) and corresponding decrease in men (49.5 percent to 46.0 percent). The number of participants in Phase III intramural clinical research increased from 27,044 to 31,476.

Trend Report on NIH Aggregate Population Data FY 1995–2006

The following section was a new addition to the FY 2005 and 2006 Comprehensive Report. In the FY 2005 and 2006 Comprehensive Report, Tables 5 to 11 provide trend data on the collection and reporting of human subject participation in NIH-funded clinical research, which includes Phase III clinical studies. Trend data are also provided in foreign and domestic participation. The report notes that trend data varies over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; (3) and the subtraction of studies that are no longer reported.

Table 5 in the FY 2005 and 2006 Comprehensive Report is a 12-year summary report showing a steady increase in protocols and enrollment data collected. The number of protocols with enrollment increased from 3,188 in FY 1995 to 10,758 in FY 2006, a 3.4-fold increase. Reported enrollment increased from approximately 1.0 million in FY 1995 to 14.8 million in FY 2006, a 14.5-fold increase. Minority enrollment increased from approximately 0.4 million in FY 2002 to 6.4 million in FY 2006, a 17.1-fold increase in minority representation in NIH clinical research. Over the last five years, the total number of protocols reported with enrollment data has leveled off at about 10,000 protocols per year. (See also Table 9.)

With the deployment of a new population tracking system in 2002 and the requirement to report data using a new format, the NIH was able to report domestic and foreign data in a better way. Thus, trend data are now available for domestic and foreign protocols and participation beginning in FY 2002. Domestic enrollment increased from 10.2 million in FY 2002 to 11.4 million in FY 2006, a 1.1-fold increase. Foreign enrollment increased from 0.9 million in FY 2002 to 3.4 million in FY 2006, a 3.6-fold increase. Overall, the total enrollment has increased with domestic participation averaging between 75.9 percent to 91.5 percent and foreign participation averaging between 8.5 and 24.1 percent. In FY 2006, domestic and foreign enrollment was 77.0 percent and 23.0 percent respectively.

Table 6 in the FY 2005 and 2006 Comprehensive Report is a summary report of all extramural and intramural clinical research by sex/gender and minority representation following the old and new data formats for domestic and foreign studies. The report demonstrates that female participation in all extramural and intramural research generally averaged between 51.7 percent and 63.9 percent; male participation in all extramural and intramural research averaged between 34.9 percent and 45.0 percent. Overall minority participation in all extramural and intramural clinical research averaged between 31 percent and 43 percent. Table 6E of the FY 2005 and 2006 Comprehensive Report provides a comparison of domestic and foreign participation between FY 2002 and 2006. The vast majority of protocols are domestic (approximately 94 to 96 percent) of the total clinical research protocols. While the number of foreign protocols has increased,

they incorporate only about 4 to 6 percent of the total clinical research protocols with enrollment. Table 6F of that report shows domestic and foreign enrollment for the five-year period. Domestic minority enrollment varied between 24.1 percent and 28.9 percent of total domestic participation, while foreign minority enrollment varied between 82.2 percent and 90.9 percent of total foreign participation. (See also Table 10 below.)

In the FY 2005 and 2006 Comprehensive Report, Table 7 (see Table 11) is a summary report of NIH-funded Phase III extramural and intramural clinical research by sex/gender and minority representation following the old and new data reporting formats for domestic and foreign studies. The report demonstrates that female participation in NIH-funded Phase III extramural and intramural clinical research generally averaged between 54.1 and 74.8 percent, and male participation in NIH-funded Phase III extramural and intramural clinical research averaged between 24.3 and 44.6 percent. Overall minority participation in NIH-funded Phase III extramural and intramural clinical research increased from 26.9 to 33.5 percent. Table 7E in that report (see Table 11E) provides a comparison of domestic and foreign participation between FY 2002 and 2006. The vast majority of protocols are domestic (75.5 percent and 95.8 percent) of the total clinical research protocols. Although the number of foreign protocols has decreased, they incorporate only about 4.2 percent to 9.6 percent of the total clinical research protocols with enrollment in the last three years. Table 7F of the report (see Table 11F) shows domestic and foreign enrollment for the five-year period. Domestic minority enrollment varied between 20.7 and 25.4 percent of total domestic participation, while foreign minority enrollment in NIH-funded Phase III clinical research varied between 48.4 and 85.2 percent of total foreign participation. Comparing both domestic and foreign Phase III enrollment over the five-year period shows that the small percentage of foreign protocols (9.6 percent) in FY 2006 accounts for a significant proportion (19.8 percent) of the total enrollment.

Tables 8 through 11 of the FY 2005 and 2006 Comprehensive Report provide summary reports of domestic and foreign participation for NIH-funded clinical research and NIH-funded Phase III clinical research. (See Tables 12 through 15.) For extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation averaged between 61.8 and 67.3 percent while male participation averaged between 31.2 and 36.9 percent. (See Table 12 and Table 8 of the FY 2005 and 2006 Comprehensive Report.) For NIH-funded Phase III extramural and intramural clinical research, domestic participants enrolled in domestic protocols, female participation averaged between 54.8 and 64.6 percent while male participation averaged between 34.4 and 44.8 percent. (See Table 13 and Table 9 of the FY 2005 and 2006 Comprehensive Report.) For all extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 39.2 to 58.5 percent while male participation varied from 40.1 to 60.4 percent. (See Table 10 of the report.) For NIH-funded Phase III extramural and intramural clinical research, foreign participants enrolled in foreign protocols, female participation varied from 47.4 to 56.7 percent while male participation varied from 42.0 to 52.5 percent. (See Table 15 and Table 11 of the FY 2005 and 2006 Comprehensive Report.)

Conclusion and Current Status

NIH staff continues 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 proposals throughout the application process. Review officials introduce and discuss with reviewers the guidelines and instructions for reviewing the applications' information on inclusion of women and minorities in clinical research as well as the instructions and requirements for designing Phase III clinical trials so that 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 are required to withhold funding until the principal investigator has satisfactorily addressed the policy requirements.

TABLE 5. Summary of NIH Clinical Research Reported in FY 2006: Total Number of Protocols and Enrollment by Sex and Domestic vs. Foreign Protocols

5A. PROTOCOLS REPORTED	ALL CLINICAL STUDIES*	DOMESTIC	%	FOREIGN	%
Protocols with Enrollment	10,758	10,294	95.7%	464	4.3%
%	70.2%	70.3%		69.3%	
Protocols with Zero Enrollment†	4,562	4,356	95.5%	206	4.5%
%	29.8%	29.7%		30.7%	
Total Number Protocols	**15,320**	**14,650**	**95.6%**	**670**	**4.4%**
%	100.0%	100.0%		100.0%	

* Clinical research studies include non-intervention clinical research, clinical trials, epidemiologic studies, behavioral studies, database studies, etc., based on the NIH definition of clinical research. All Clinical Studies include NIH-defined Phase III clinical trials.

† Enrollment data have not yet been submitted.
See comments below.

5B. ENROLLMENT REPORTED	ALL CLINICAL STUDIES	DOMESTIC	%	FOREIGN	%
Females Enrolled	9,473,273	7,684,453	81.1%	1,788,820	18.9%
%	63.9%	67.3%		52.5%	
Males Enrolled	5,172,205	3,566,577	69.0%	1,605,628	31.0%
%	34.9%	31.2%		47.2%	
Sex of Subject Unknown	185,452	174,671	94.2%	10,781	5.8%
%	1.3%	1.5%		0.3%	
Total Subjects Enrolled	**14,830,930**	**11,425,701**	**77.0%**	**3,405,229**	**23.0%**
%	100.0%	100.0%		100.0%	

See comments below.

5C. MINORITY ENROLLMENT REPORTED	ALL CLINICAL STUDIES	DOMESTIC	%	FOREIGN	%
Minority Total‡	6,388,316	3,301,135	51.7%	3,087,181	48.3%
% Minority Enrollment	43.1%	28.9%		90.7%	

‡ See Appendix H of the FY 2005-2006 Comprehensive Report for the Race and Ethnicity categories included in Minority Enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.
See comments below.

NOTE: Percentages are reported with one decimal point; due to rounding, adding percentages may not equal 100%.

Comments on Table 5A: Protocols Reported

1.The total number of protocols reported in the NIH database in FY 2006 was 15,320; of these 10,758 (70.2%) reported subject enrollment.
2. Subsequent tables reporting Enrollment Reported are based on the 10,758 protocols reporting subject enrollment or a defined subset.
3. Protocols with zero enrollment (data not yet submitted) are not included in subsequent tables reporting Enrollment Reported.
4. Domestic protocols made up the vast majority of protocols (14,650 or 95.6%). Of these, 10,294 (70.3%) reported domestic subject enrollment.
5. Clinical research involving both domestic and foreign sites is reported as separate Domestic and Foreign protocols in subsequent tables.

Comments on Table 5B: Enrollment Reported

1. The total Enrollment Reported in the NIH database in FY 2006 was 14,830,930 subjects in 10,758 protocols with enrollment.
2. Females made up 63.9% (9.5 million) of the total subjects enrolled while males made up 31.2% (5.2 million) with 1.3% unknown.
3. The total Domestic Enrollment reported was 11,425,701 (77%).
4. Females made up 67.3% (7.7 million) of the domestic subjects enrolled while males made up 31.2% (3.56 million) with 1.5% (0.17 million) unknown.

Comments on Table 5C: Minority Enrollment Reported

1. Minorities made up 43.1% (6.4 million) of the total subjects enrolled.
2. Minorities made up 28.9% (3.3 million) of the Domestic enrollment.
3. The Total Minority Enrollment was made up of 51.7% Domestic and 48.3% Foreign enrollment. The small percentage of foreign protocols (4.0%) accounts for a significant proportion (48.3%) of the total minority enrollment.

Table 6. Overview of NIH Extramural and Intramural Clinical Research Reported in FY 2006: Number of Sex-Specific Protocols and Domestic vs. Foreign Protocols

6A. PROTOCOLS REPORTED	ALL CLINICAL STUDIES	DOMESTIC EXTRAMURAL	%	DOMESTIC INTRAMURAL	%	FOREIGN EXTRAMURAL	%	FOREIGN INTRAMURAL
Number protocols reporting females only	1,338	1,162	86.8	124	9.3	46	3.4	6
%	8.7%	9.0%		7.3%		8.1%		6.1%
Number protocols reporting males only	581	468	80.6	93	16.0	17	2.9	3
%	3.8%	3.6%		5.5%		3.0%		3.0%
Number protocols with both males and females reporting*	8,839	7,221	81.7	1,226	13.9	321	3.6	71
%	57.7%	55.8%		72.2%		56.2%		71.7%
Total Protocols with Enrollment	**10,758**	**8,851**	**82.3**	**1,443**	**13.4**	**384**	**3.6**	**80**
%	70.2%	68.0%		84.9%		67.3%		80.8%
Number protocols with zero enrollment†	4,562	4,100	89.9	256	5.6	187	4.1	19
%	29.8%	31.7%		15.1%		32.7%		19.2%
Total Protocols	**15,320**	**12,951**	**84.5**	**1,699**	**11.1**	**571**	**3.7**	**99**
	100.0%	100.0%		100.0%		100.0%		100.0%

* Number of protocols with both males and females reporting excludes sex-specific protocols.

† Enrollment data have not yet been submitted.

Comments on Table 6A, Total Number of Protocols with Enrollment Reported

1. Female only protocols: There were 1,338 protocols reporting females only, representing 12.4% (1,338/10,758) of protocols with enrollment. 90% were Extramural projects (1,162 + 46); 10% were NIH Intramural projects (124 + 6). 96% were Domestic protocols (1,162 + 124); 4% were Foreign protocols (40 + 6).
2. Male only protocols: There were 581 protocols reporting males only, representing 5% (558/10,758) of protocols with enrollment. 83% were Extramural projects (468 + 17); 17% were NIH Intramural projects (93 + 3). 97% were Domestic protocols (468 + 93); 3% were Foreign protocols (17 + 3).
3. Protocols reporting both females and males (excluding sex-specific protocols): There were 8,839 protocols reporting both female and male participants, representing 82% (8,839/10,758) of the total number of protocols. 85% were Extramural projects (7,221 + 321); 15% were NIH Intramural projects (1,225 + 71).

6B. Enrollment Reported	All Clinical Studies	Domestic Extramural	%	Intramural	%	Foreign Extramural	%	Intramural	%
In protocols reporting females only	4,120,055	3,678,382	89.3	202,024	4.9	115,369	2.8	124,280	3.0
%	27.8%	36.9%		13.9%		3.8%		35.0%	
In protocols reporting males only	336,717	274,774	81.6	3,294	1.0	32,552	9.7	26,097	7.8
%	2.3%	2.8%		0.2%		1.1%		7.3%	
In protocols excluding male-only and female-only protocols	10,374,158	6,018,281	58.0	1,248,946	12.0	2,902,088	28.0	204,843	2.0
%	69.9%	60.4%		85.9%		95.2%		57.7%	
Total Enrollment	**14,830,930**	**9,971,437**	**67.2**	**1,454,264**	**9.8**	**3,050,009**	**20.6**	**355,220**	**2.4**
%	100.0%	100.0%		100.0%		100.0%		100.0%	

See comments below.

6C. Minority Enrollment Reported*	All Clinical Studies	Domestic Extramural	%	Intramural	%	Foreign Extramural	%	Intramural	%
Minority Totals for All Studies	6,388,316	3,102,731	48.6	198,404	3.1	2,878,826	45.1	208,355	3.3
% Minority Enrollment	43.1%	31.1%		13.6%		94.4%		58.7%	

* See Appendix H of the FY 2005 and 2006 Comprehensive Report for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Comments on Table 6B: Total Enrollment Reported

1. In female only protocols: There were approximately 4.1 million females, representing 28% of total enrollment. 92.1% were in Extramural projects; 7.9% were in NIH Intramural projects. 94.2% were in Domestic protocols; 5.8% were in Foreign protocols.
2. In male only protocols: There were approximately 336, 717 males, representing 2.3% of total enrollment. 91.3% were in Extramural projects; 18.8% were in NIH Intramural projects. 82.6% were in Domestic protocols; 17.4% were in Foreign protocols.
3. In protocols reporting both females and males (excluding sex-specific studies): There were approximately 10,374 subjects, representing 70% of total enrollment. 86% were in Extramural projects; 14% were in NIH Intramural projects. 70% were in Domestic protocols; 30% were in Foreign protocols. 96% were in Domestic protocols (7,221 + 1,226); 4% were in Foreign protocols (321 + 71).

Comments on Table 6C: Minority Enrollment Reported

1. Total minority enrollment was 43.1% of total enrollment (14.8 million). Total minority enrollment for Domestic protocols was 28.9% (3,301,135/11,425,701). Total Domestic minority enrollment was 51.7% (3,301,135/6,388,316). Total Foreign minority enrollment was 48.3% (3,087,181/6,388,316). Total Extramural projects minority enrollment was 40.33% (5,981,557/14,830,930). Total Intramural project minority enrollment was 2.74% (406,759/14,830,930).

TABLE 7. Summary of NIH Phase III Clinical Research Reported in FY 2006: Total Number of Protocols and Enrollment by Sex and Domestic vs. Foreign Protocols

7A. PROTOCOLS REPORTED	ALL PHASE III CLINICAL TRIALS*	DOMESTIC	%	FOREIGN	%
Protocols with Enrollment	624	564	90.4%	60	9.6%
%	82.1%	82.0%		83.3%	
Protocols with Zero Enrollment†	136	124	91.2%	12	8.8%
%	17.9%	18.0%		16.7%	
Total Number Protocols	**760**	**688**	**90.5%**	**72**	**9.5%**
%	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.

† Enrollment data have not yet been submitted.
See comments below.

7B. ENROLLMENT REPORTED	TOTAL PHASE III CLINICAL TRIALS*	DOMESTIC	%	FOREIGN	%
Females Enrolled	314,066	258,467	82.3%	55,599	17.7%
%	62.9%	64.6%		56.1%	
Males Enrolled	179,975	137,621	76.5%	42,345	23.5%
%	36.0%	34.4%		42.7%	
Sex of Subject Unknown	5,389	4,209	78.1%	1,180	0.0%
%	1.1%	1.1%		1.2%	
Total Subjects Enrolled	**499,430**	**400,297**	**80.2%**	**99,133**	**19.8%**
%	100.0%	100.0%		100.0%	

* See definition of NIH-defined Phase III clinical trials in * footnote to Table 7A above.
See comments below.

NOTE: Percentages are reported with one decimal point. Due to rounding, adding percentages may not equal 100%.

Comments on Table 7A: Total Number of Protocols

1. The total number of NIH-defined Phase III clinical protocols reported in the NIH database in FY 2006 was 760; of these, 624 (82.1%) reported subject enrollment.
2. Subsequent Tables reporting Enrollment Reported are based on the 624 protocols reporting subject enrollment or a defined subset.
3. Protocols with zero enrollment (data not yet submitted) are not included in subsequent tables reporting Enrollment Reported.
4. Domestic protocols made up the vast majority of protocols (688, 90.5%); of these, 564 (82%) reported Domestic subject enrollment.
5. Clinical research involving both Domestic and Foreign sites are reported as separate Domestic and Foreign protocols in subsequent tables.

Comments on Table 7B: Total Enrollment Reported

1. The total Enrollment Reported in NIH-defined Phase III protocols in the NIH database in FY 2006 was 499,430 subjects in 624 protocols.
2. Females made up 62.9% (314,068) of the total subjects enrolled while males made up 36.0% (179,975) with 1.1% (5,389) unknown.
3. Minorities made up 33.5% (167,446) of the total subjects enrolled.
4. The total Domestic enrollment reported was 400,297 (80.2%).
5. Females made up 64.6% (258,467) of the Domestic subjects enrolled while males made up 34.4% (137,621) with 1.1% (4,209) unknown.

7C. Minority Enrollment Reported†	Total Phase III Clinical Trials*	Domestic	%	Foreign	%
Minority Total for All Phase III Studies	167,446	83,034	49.6%	84,412	50.4%
%	33.5%	20.7%		85.2%	

* See definition of NIH-defined Phase III clinical trials in * footnote to Table 7A above.

† See Appendix H of the FY 2005 and 2006 Comprehensive Report for the Race and Ethnicity categories included in Minority Enrollment Data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.

Comments on Table 7C: Minority Enrollment Reported

1. Minorities made up 33.5% of total subjects enrolled.
2. Minorities made up 20.7% (83,034) of the Domestic enrollment (400,297).
3. The Total Minority Enrollment was made up of 49.6% Domestic and 50.4% Foreign enrollment.

Table 8. Overview of NIH Phase III Extramural and Intramural Clinical Research Reported in FY 2006: Number of Sex-Specific Protocols and Enrollment and Domestic vs. Foreign Protocols

8A. Protocols Reported	All Phase III Clinical Trails*	Domestic Extramural	%	Domestic Intramural	%	Foreign Extramural	%	Foreign Intramural	%
Protocols reporting females only	118	101	85.6	2	1.7	14	11.9	1	0.8
%	15.5%	15.8%		4.2%		20.9%		20.0%	
Protocols reporting males only	47	39	83.0	4	8.5	4	8.5	0	0.0
%	6.2%	6.1%		8.3%		6.0%		0.0%	
Protocols with both males and females reporting†	459	384	83.7	34	7.4	38	8.3	3	0.07
%	60.4%	60.0%		70.8%		56.7%		60.0%	
Total Protocols with Enrollment	**624**	**524**	**84.0**	**40**	**6.4**	**56**	**9.0**	**4**	**0.6**
%	82.1%	82.0%		83.3%		83.6%		80.0%	
Phase III Protocols with Zero Enrollment†	136	116	85.3	8	5.9	11	8.1	1	0.0
%	17.9%	18.1%		16.7%		16.4%		20.0%	
Total Phase III Protocols	**760**	**640**	**84.2**	**48**	**6.3**	**67**	**8.8**	**5**	**0.7**
%	100.0%	100.0%		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.

† These exclude sex-specific protocols.

‡ Enrollment data have not yet been submitted.

See comments on the following page.

Comments on Table 8A: Total Number of Phase III Protocols with Enrollment

1. Female only: There were 118 protocols reporting females only, representing 19% (118/624) of protocols with enrollment and 15.5% of the total number of protocols. 97% were Extramural projects (115); 3% were NIH Intramural projects (3). 87% were Domestic protocols (103); 13% were Foreign protocols (15).
2. Male only: There were 47 protocols reporting males only, representing 8% (47/624) of protocols with enrollment and 6.2% of the total number of protocols. 91% were Extramural projects (43); 9% were NIH Intramural projects (4). 91% were Domestic protocols (43); 9% were Foreign protocols (41).
3. Protocols reporting both females and males (excluding sex-specific protocols): There were 459 protocols reporting both males and females, representing 60.4% of the total number of protocols. 92.0% were Extramural projects (422); 8.0% were NIH Intramural projects (37). 91% were Domestic protocols (418); 9.0% were Foreign protocols (41).

8B. ENROLLMENT REPORTED	ALL PHASE III CLINICAL TRIALS	DOMESTIC EXTRAMURAL	%	DOMESTIC INTRAMURAL	%	FOREIGN EXTRAMURAL	%	FOREIGN INTRAMURAL	%
Protocols reporting females only	167,624	148,185	88.4	4	0.0	17,195	10.3	2,240	1.3
%	33.6%	38.4%		0.0%		21.0%		13.0%	
Protocols reporting males only	27,723	23,312	84.1	177	0.6	4,234	15.3	0	0.0
%	5.6%	6.0%		1.2%		5.2%		0.0%	
Protocols with both males and females reporting*	304,083	214,619	70.6	14,000	4.6	60,409	19.9	15,055	5.0
%	60.9%	55.6%		98.7%		73.8%		87.0%	
Total Subjects Enrolled	**499,430**	**386,116**	**77.3**	**14,181**	**2.8**	**81,838**	**16.4**	**17,295**	**3.5**
%	100.0%	100.0%				100.0%		100.0%	

* Excludes female-only and male-only enrollment protocols.

Comments on Table 8B: Total Enrollment Reported

1. Female only protocols: There were approximately 167,624 females, representing 33.6% of the total enrollment. 98.7% (165,380) were in Extramural projects; 1.3% (2,244) were in NIH Intramural projects. 88.4% (148,189) were in Domestic protocols; 11.7% (19,435) were in Foreign protocols.
2. Male only protocols: There were approximately 27,723 males, representing 5.6% of total enrollment. 99.4% (27,546) were in Extramural projects; 0.6% (177) were in NIH Intramural projects. 84.7% (23,489) were in Domestic protocols; 15.3% (4,234) were in Foreign protocols.
3. Both female and male protocols (excluding sex-specific protocols): There were approximately 304,083 subjects, representing 60.9% of total enrollment. 90.5% (275,028) were in Extramural projects; 9.5% (29,055) were in NIH Intramural projects. 75.2% (228,619) were in Domestic protocols; 24.8% (75,464) were in Foreign protocols.

8C. Minority Enrollment Reported*	All Phase III Clinical Trials	Domestic Extramural	%	Domestic Intramural	%	Foreign Extramural	%	Foreign Intramural	%
Minority Total for all Phase III Trials	167,446	80,622	48.1	2,412	1.4	69,820	41.7	14,592	8.7
%	33.5%	20.9%		17.0%		85.3%		84.4%	
%	100.0%	100.0%		100.0%		100.0%		100.0%	

* See Appendix H of the FY 2005 and 2006 Comprehensive Report for the Race and Ethnicity categories included in Minority Enrollment data from the 1977 and 1997 U.S. OMB race/ethnicity categories. Foreign enrollment was reported using the U.S. race and ethnicity categories.
See comments below.

Comments on Table 8C: Minority Enrollment Reported

1. Total minority enrollment was 33.5% (167,446) of total enrollment (499,430). Total minority enrollment in Extramural protocols (150,442) was 30.1% of total enrollment (499,430) and 89.9% of total minority enrollment (167,446). Total minority enrollment in Intramural projects (17,004) was 3.4% of total enrollment (499,430) and 10.15% of total minority enrollment (167,446).
2. Total minority enrollment in Domestic protocols (83,034) was 20.7% of total Domestic enrollment (400,297) and 49.6% of total minority enrollment (167,446).
3. Total minority enrollment in Foreign protocols (84,412) was 85.15% of total Foreign enrollment (99,133) and 50.4% of total minority enrollment (167,446).

Table 9: NIH Twelve Year Trends for Protocol and Enrollment Data: 1995-2006

Table 9A: Twelve Year Increases in Protocols and Enrollment Data

FY Reported	1995	2006	Relative Increase 2006/1995
Total Protocols with Enrollment	**3,188**	**10,758**	**3.4**
Total Enrollment	1,021,493	14,830,930	14.5
Total Minority Enrollment	374,433	6,388,316	17.1
% Minority	36.7%	43.1%	1.2
FY Reported	**2002**	**2006**	**Relative Increase 2006/2002**
Total Domestic Enrollment	10,192,401	11,425,701	1.1
Total Foreign Enrollment	946,083	3,405,229	3.6

See Note and Comments on following page.

TABLE 9B: TWELVE YEAR SUMMARY OF TOTAL NUMBER OF PROTOCOLS REPORTED: FY 1995-2006

FY REPORTED	FY FUNDED	N PROTOCOLS*	N DOMESTIC PROTOCOLS†	N FOREIGN PROTOCOLS†	% DOMESTIC PROTOCOLS	PROTOCOL FORM‡
1995	1994	3,188				OLD
1996	1995	6,036				OLD
1997	1996	5,692				OLD
1998	1997	7,602				OLD
1999	1998	8,285				OLD
2000	1999	9,390				OLD
2001	2000	10,212				OLD
2002	2001	8,945	8,463	482	94.6%	OLD + NEW
2003	2002	10,216	9,578	638	93.8%	OLD + NEW
2004	2003	10,125	9,760	365	96.4%	OLD + NEW
2005	2004	10,233	9,862	371	96.4%	OLD + NEW
2006	2005	10,758	10,294	464	95.7%	OLD + NEW

* Number of protocols with enrollment data (OLD + NEW Forms).
† Includes only protocols with enrollment data.
‡ Data have been reported using a combined race/ethnicity format (OLD form) since 1995. New protocols began reporting separate race and ethnicity data in FY 2002 (NEW form). During 2002-2006, data have been reported using both OLD and NEW forms.
See Note and Comments below.

GRAPH 9B: TOTAL PROTOCOLS BY YEAR REPORTED: OLD FORM AND OLD + NEW FORMS

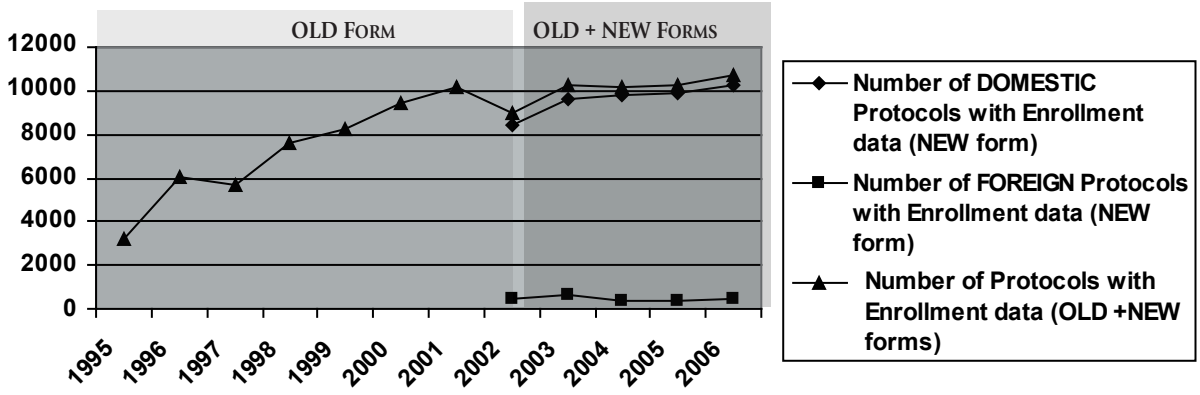
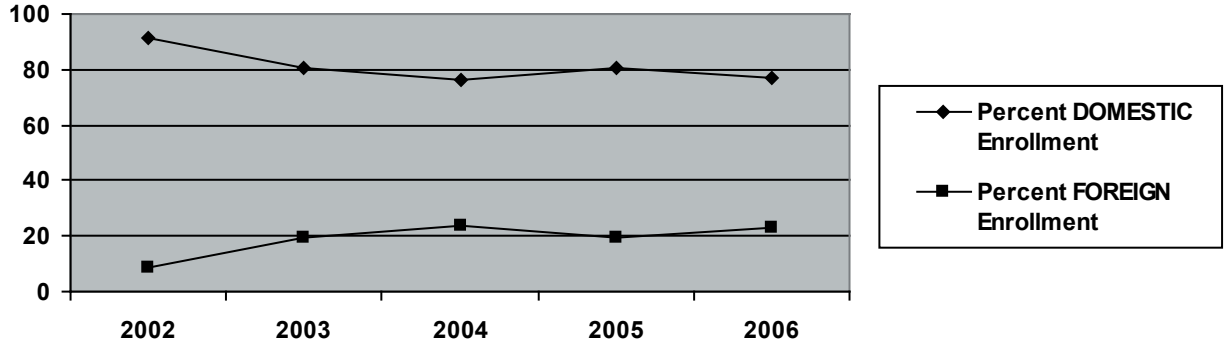


TABLE 9C: COMPARISON OF DOMESTIC AND FOREIGN ENROLLMENT REPORTED IN FY 2002-2006

FY REPORTED	FY FUNDED	TOTAL ENROLLMENT*	TOTAL DOMESTIC ENROLLMENT	% DOMESTIC ENROLLMENT	TOTAL FOREIGN ENROLLMENT	% FOREIGN ENROLLMENT
2002	2001	11,138,484	10,192,401	91.5%	946,083	8.5%
2003	2002	14,772,254	11,911,357	80.6%	2,860,897	19.4%
2004	2003	18,923,920	14,359,793	75.9%	4,564,127	24.1%
2005	2004	15,722,752	12,669,858	80.6%	3,052,894	19.4%
2006	2005	14,830,930	11,425,701	77.0%	3,405,229	23.0%

* Total enrollment data is based on OLD and NEW forms.
See Note and Comments below.

GRAPH 9C: PERCENT COMPARISON OF DOMESTIC AND FOREIGN ENROLLMENT



NOTE: Trend data varies over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported.

Comments on Table 9A: Twelve Year Increases in Protocols and Enrollment Data

1. There was a 3.4 fold increase in protocols with enrollment reported from 1995 to 2006 from 3,188 protocols to 10,758 protocols.
2. There was a 14.5 fold increase in enrollment reported from 1995 to 2006 from approximately 1 million to 15 million.
3. There was a 17.1 fold increase in minority enrollment from 1995 to 2006 from approximately 0.4 million to 6.4 million.
4. Domestic and Foreign data were reported for FY 2002-2006 and showed a 1.1 fold increase in Domestic enrollment (from 10.2 million to 11.4 million) and a 3.6 fold increase in Foreign enrollment (from 0.95 million to 3.4 million).
5. See Table 10 for 12 year enrollment totals for 1995-2006.

Comments on Table 9B: Twelve Year Summary of Total Number of Protocols Reported: FY 1995-2006

1. Table 9B and Graph 9B provide the number of OLD and NEW protocols year by year (1995-2006) and the distribution between Domestic and Foreign protocols for years 2002-2006.
2. The total number of protocols reported with enrollment has leveled off at about 15,000 over the last 4 years.
3. The vast majority of protocols were for domestic studies for 2002-2006, ranging from 93.8% to 96.4% of protocols.

Comments on Table 9C: Comparison of Domestic and Foreign Enrollment in FY 2002-2006

1. Overall total enrollment has increased as well as total Domestic and Foreign enrollment during the last 5 years. The percentage of Domestic enrollment has decreased to approximately 79% as the Foreign enrollment has increased to approximately 21%.

Table 10. NIH Twelve Year Minority Trend Summary of NIH Extramural and Intramural Clinical Research Reported in FY 1995-2006: Enrollment by Race and Ethnicity

TABLE 10A: TWELVE YEAR SUMMARY TOTALS: ENROLLMENT BY SEX/GENDER AND MINORITY CATEGORIES IN ALL PROTOCOLS (OLD AND NEW FORMS)

FY REPORTED	FY FUNDED	FORM	FEMALES	MALES	UNKNOWN	TOTAL SUBJECTS*	SUBTOTAL MINORITY†	N PROTOCOLS‡
1995	1994	OLD	528,421	459,921	33,151	1,021,493	374,433	3,188
	%		51.7	45.0	3.2	100.0	36.7	
1996	1995	OLD	4,130,385	2,583,865	91,054	6,805,304	2,125,958	6,036
	%		60.7	38.0	1.3	100.0	31.2	
1997	1996	OLD	3,320,610	1,930,783	65,540	5,316,933	1,709,223	5,692
	%		62.5	36.3	1.2	100.0	32.2	
1998	1997	OLD	4,246,130	2,716,880	115,566	7,078,576	2,923,662	7,602
	%		60.0	38.4	1.6	100.0	41.3	
1999	1998	OLD	5,102,306	2,712,068	169,863	7,984,237	3,108,228	8,285
	%		63.9	34.0	2.1	100.0	38.9	
2000	1999	OLD	5,585,042	3,919,065	64,990	9,569,097	3,406,297	9,390
	%		58.4	41.0	0.7	100.0	35.6	
2001	2000	OLD	6,808,822	4,740,887	44,547	11,594,256	3,619,119	10,212
	%		58.7	40.9	0.4	100.0	31.1	
2002	2001	OLD + NEW	7,155,549	3,904,560	78,375	11,138,484	3,666,880	8,945
	%		64.2	35.1	0.7	100.0	32.9	
2003	2002	OLD + NEW	8,514,481	6,121,496	136,277	14,772,254	5,387,692	10,216
	%		57.6	41.4	0.9	100.0	36.5	
2004	2003	OLD + NEW	10,889,097	7,741,892	292,931	18,923,920	7,611,611	10,125
	%		57.5	40.9	1.5	100.0	40.2	
2005	2004	OLD + NEW	9,503,922	5,941,907	276,923	15,722,752	6,245,436	10,233
	%		60.4	37.8	1.8	100.0	39.7	
2006	2005	OLD + NEW	9,473,273	5,172,205	185,452	14,830,930	6,388,316	10,758
	%		63.9	34.9	1.25	100.0	43.1	

* Includes OLD and NEW forms.

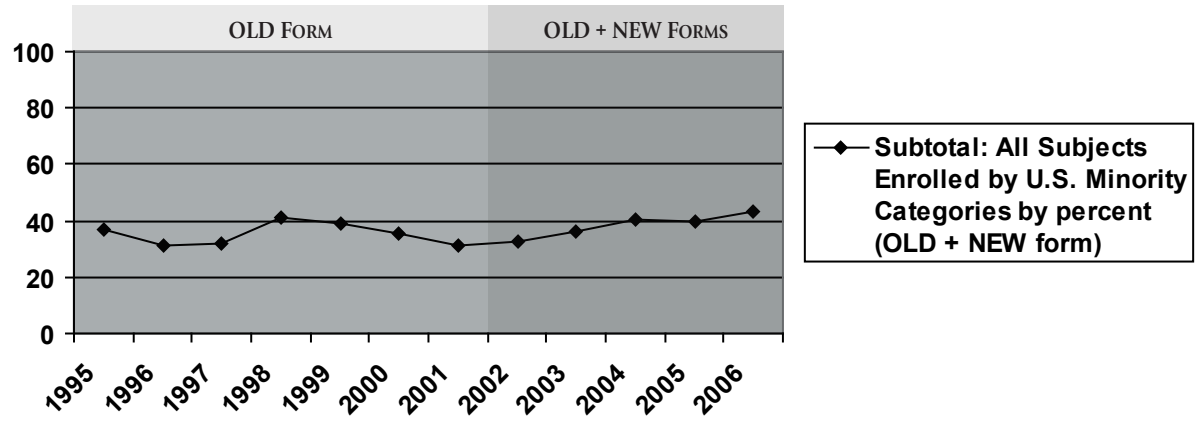
†These data are a subtotal of all subjects enrolled by U.S. minority categories.

‡ The number of protocols is calculated from those with enrollment data (OLD and NEW forms).
See Note and Comments Below

Comments on Table 10A:

1. Table 10A summarizes enrollment by sex/gender and minority race/ethnicity categories for the twelve year reporting period (1995-2006). The data are compiled from Tables 10B, 10C, and 10D, which provide the detailed distributions by sex/gender and race/ethnicity using the OLD enrollment form (Table 10B) and the NEW enrollment form (Table 10C and 10D).
2. The Race and Ethnicity data in the OLD Form and the NEW Form cannot be combined by individual race and ethnicity categories because the categories reflect the different OMB formats used based on the 1977 OMB standards (OLD Form) and the 1997 OMB standards (NEW Form).

GRAPHS 10A(1): PERCENTAGE OF TOTAL MINORITY ENROLLMENT BY YEAR REPORTED



GRAPH 10A(2): PERCENTAGE OF SEX/GENDER ENROLLMENT BY YEAR REPORTED

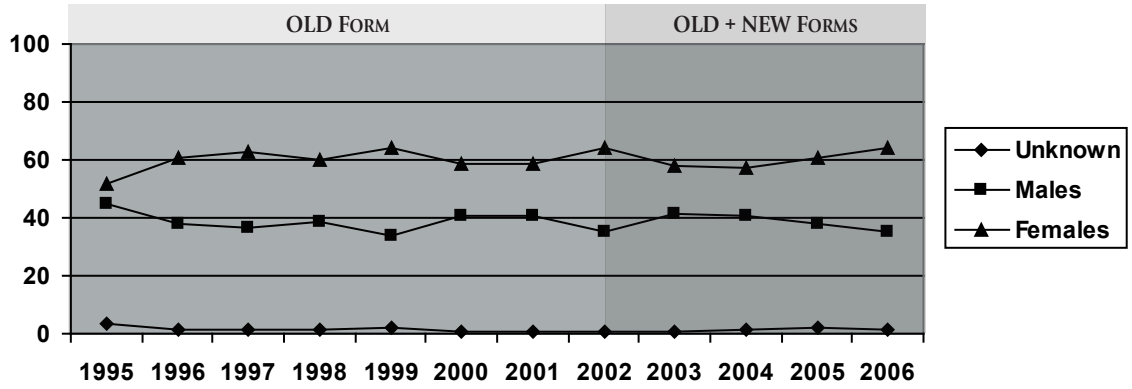


TABLE 10B: OLD FORM: TOTAL OF ALL SUBJECTS REPORTED USING THE 1977 OMB STANDARDS IN A COMBINED RACE/ETHNICITY FORMAT

FY REPORTED/ FUNDED	AMERICAN INDIAN/ ALASKA NATIVE	ASIAN/ PACIFIC ISLANDER	BLACK OR AFRICAN AMERICAN	HISPANIC, NOT WHITE	WHITE	UNKNOWN OR OTHER	TOTAL	SUBTOTAL*	N PROTOCOLS†
1995/1994	11,221	38,952	234,976	89,284	540,313	106,747	1,621,493	374,433	3,188
%	1.1	3.8	23.0	8.7	52.9	10.5	100.0	36.7	
1996/1995	146,319	617,211	823,102	539,326	4,114,249	565,097	6,805,304	2,125,958	6,036
%	2.2	9.1	12.1	7.9	60.5	8.3	100.0	31.2	
1997/1996	36,638	321,479	864,102	487,004	3,199,778	407,932	5,316,933	1,709,223	5,692
%	0.7	6.0	16.3	9.2	60.2	7.7	100.0	32.1	
1998/1997	85,957	1,237,030	1,096,218	504,457	3,713,759	441,155	7,078,576	2,923,662	7,602
%	1.2	17.5	15.5	7.1	52.5	6.2	100.0	41.3	
1999/1998	71,436	1,429,022	1,081,210	526,560	4,470,966	405,043	7,984,237	3,108,228	8,285
%	0.9	17.9	13.5	6.6	56.0	5.1	100.0	38.9	
2000/1999	82,728	1,525,392	1,209,769	588,408	5,588,942	573,858	9,569,097	3,406,297	9,390
%	0.9	15.9	12.6	6.1	58.4	6.0	100.0	35.6	
2001/2000	105,067	1,495,279	1,199,625	819,148	7,314,449	660,688	11,594,256	3,619,119	10,212
%	0.9	12.9	10.3	7.1	63.1	5.7	100.0	31.2	
2002/2001	45,843	1,222,296	702,234	398,657	4,044,052	321,349	6,734,431	2,369,030	6,187
%	0.7	18.1	10.4	5.9	60.1	4.8	100.0	35.2	
2003/2002	36,579	730,542	472,426	288,523	3,238,284	278,901	5,045,255	1,528,070	4,903
%	0.7	14.5	9.4	5.7	64.2	5.5	100.0	30.3	
2004/2003	29,387	307,052	342,188	214,322	2,348,529	172,130	3,413,608	892,949	2,782
%	0.9	9.0	10.0	6.3	68.8	5.0	100.0	26.2	
2005/2004	22,375	254.598	229,615	134,972	1,267,089	102,405	2,011,054	641,560	1,786
%	1.1	12.7	11.4	6.7	63.0	5.1	100.0	31.9	
2006/2005	19,648	131,786	148,948	78,596	883,041	63,231	1,325,250	378,978	1,391
%	1.5	9.9	11.2	5.9	66.6	4.8	100.0	28.6	

* The subtotal is calculated using the U.S. minority categories OLD form.

† The number of protocols is based on protocols with enrollment data (OLD form).

See Notes and Comments below.

Table 10C: NEW Form Part A: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats

10C(1): Total of All Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total
2002/2001	77,734	354,049	547,776	21,636	2,651,541	30,955	730,362	4,404,053
%	1.8	8.0	12.4	0.5	60.2	0.7	16.4	100.0
2003/2002	63,544	2,138,002	960,090	37,569	5,415,710	99,462	1,012,622	9,726,999
%	0.7	22.0	9.9	0.4	55.7	1.0	10.4	100.0
2004/2003	98,047	4,345,396	1,379,857	54,452	8,065,069	186,241	1,381,250	15,510,312
%	0.6	28.0	8.9	0.4	52.0	1.2	8.9	100.0
2005/2004	292,215	3,046,370	1,358,262	53,286	7,672,890	182,953	1,105,722	13,711,698
%	2.1	22.2	9.9	0.4	56.0	1.3	8.1	100.0
2006/2005	141,567	3,463,202	1,251,339	38,460	7,089,017	321,554	1,200,541	13,505,680
%	1.0	25.6	9.3	0.3	52.5	2.4	8.9	100.0

10C(2): Total of All Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
2002/2001	3,071,952	292,429	1,039,672	4,404,053
%	69.8	6.6	23.6	100.0
2003/2002	8,162,259	611,641	953,099	9,726,999
%	83.9	6.3	9.8	100.0
2004/2003	13,168,842	756,339	1,585,131	15,510,312
%	84.9	4.9	10.2	100.0
2005/2004	11,804,164	773,939	1,133,595	13,711,698
%	86.1	5.6	8.3	100.0
2006/2005	11,308,244	1,054,313	1,143,123	13,505,680
%	83.7	7.8	8.5	100.0

See Notes and Comments below.

Table 10D: NEW Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total Hispanic or Latino	Minority NEW Form A+B	N Protocol*
2002/2001	4,867	1,305	13,066	101	159,252	7,390	106,448	292,429	1,297,850	2,758
%	1.7	0.4	4.5	0.0	54.5	2.5	36.4	100.0	29.5	
2003/2002	5,400	1,953	14,566	679	350,439	28,088	210,516	611,641	3,859,622	5,313
%	0.9	0.3	2.4	0.1	57.3	4.6	34.4	100.0	39.7	
2004/2003	6,408	5,040	25,276	2,037	361,112	62,909	293,557	756,339	6,718,662	7,343
%	0.8	0.7	3.3	0.3	47.7	8.3	38.5	100.0	43.3	
2005/2004	22,739	7,816	19,446	1,981	388,874	51,166	281,916	773,938	5,603,876	8,447
%	2.9	1.0	2.5	0.3	50.2	6.6	36.4	100.0	40.9	
2006/2005	45,074	6,641	21,712	2,193	417,495	185,477	375,721	1,054,313	6,009,338	9,367
%	4.3	0.6	2.1	0.2	39.6	17.6	35.6	100.0	44.5	

*This includes the number of protocols with enrollment data (NEW Form).

Table 10E(1): Comparison of Domestic and Foreign Enrollment and Protocols with Total Enrollment for the Period FY 2002-2006

10E: Enrollment

FY Reported/ Funded	Total Enrollment*	Total Domestic Enrollment	Percent Domestic Enrollment	Total Foreign Enrollment	Percent Foreign Enrollment
2002/2001	11,138,484	10,192,401	91.5	946,083	8.5
2003/2002	14,772,254	11,911,357	80.6	2,860,897	19.4
2004/2003	18,923,920	14,359,793	75.9	4,564,127	24.1
2005/2004	15,722,752	12,669,858	80.6	3,052,894	19.4
2006/2005	14,830,930	11,425,701	77.0	3,405,229	23.0

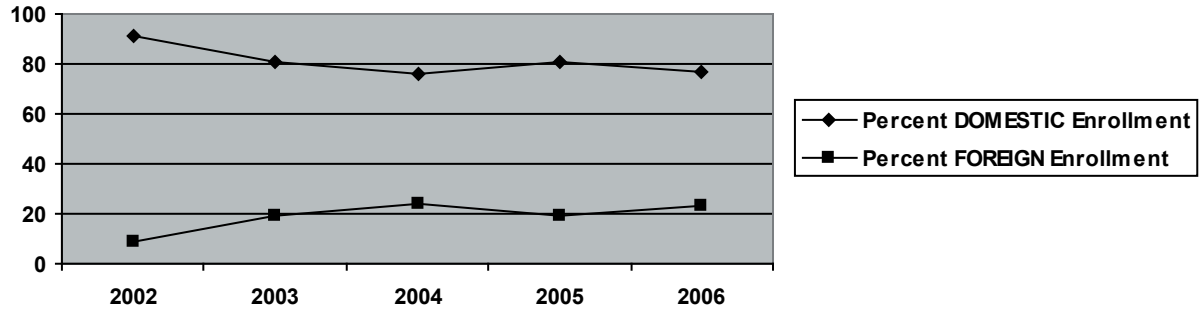
* Total enrollment includes OLD + NEW Forms.

Table 10E(2): Protocols

FY Reported/ Funded	Total Protocols w/ Enrollment*	Total Domestic Protocols	Percent Domestic Protocols	Total Foreign Protocols	Percent Foreign Protocols
2002/2001	8,945	8,463	94.6	482	5.4
2003/2002	10,216	9,578	93.8	638	6.2
2004/2003	10,125	9,760	96.4	365	3.6
2005/2004	10,233	9,862	96.4	371	3.6
2006/2005	10,758	10,294	95.7	464	4.3

*Number of protocols with enrollment data from OLD + NEW Forms.

GRAPH 10E(1): PERCENTAGE OF DOMESTIC AND FOREIGN ENROLLMENT



GRAPH 10E(2): NUMBER OF DOMESTIC AND FOREIGN PROTOCOLS

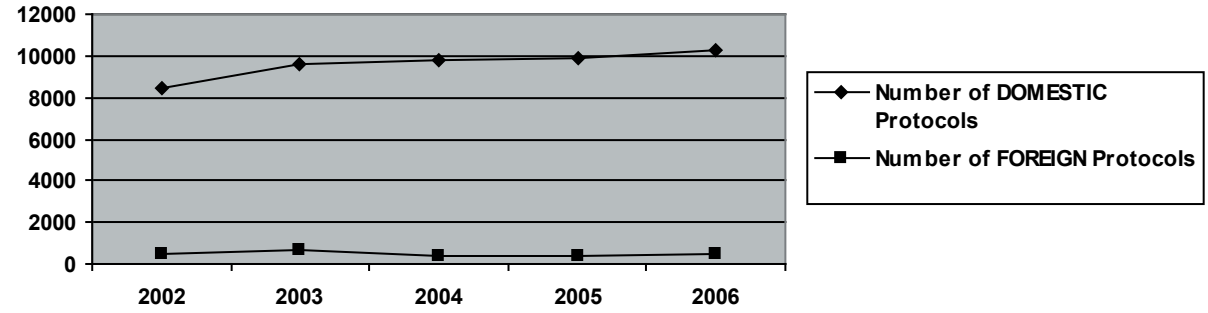
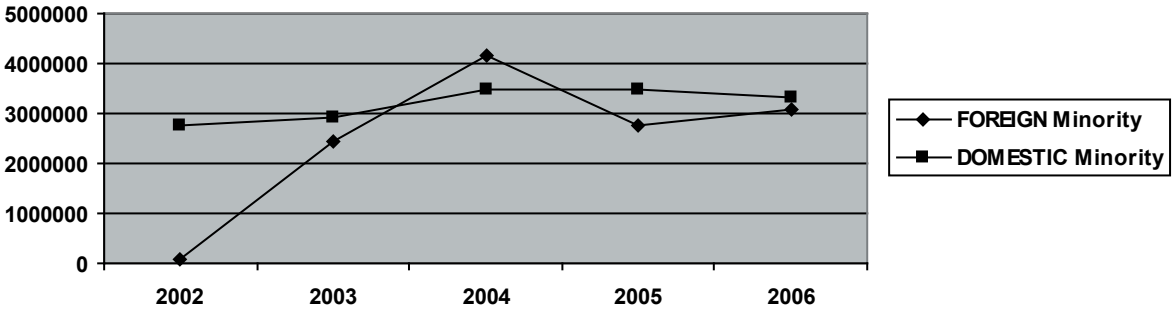


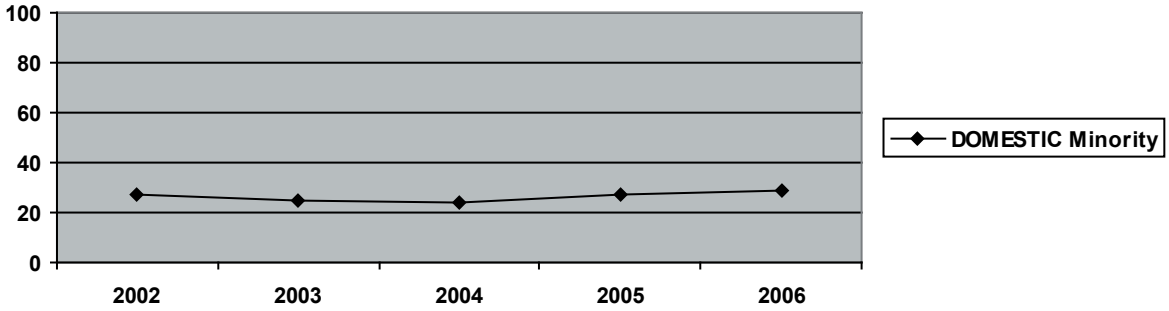
TABLE 10F: COMPARISON OF DOMESTIC AND FOREIGN MINORITY PARTICIPATION FOR FY 2002-2006

FY REPORTED/ FUNDED	FOREIGN MINORITY	FOREIGN TOTAL	DOMESTIC MINORITY	DOMESTIC TOTAL
2002/2001	777,461	946,083	2,754,820	10,149,869
%	82.2	100.0	27.1	100.0
2003/2002	2,452,329	2,860,897	2,935,363	11,911,357
%	85.7	100.0	24.6	100.0
2004/2003	4,147,255	4,564,127	3,464,356	14,359,793
%	90.9	100.0	24.1	100.0
2005/2004	2,776,565	3,052,894	3,468,864	12,669,858
%	90.9	100.0	27.4	100.0
2006/2005	3,087,181	3,405,229	3,301,135	11,425,701
%	90.7	100.0	28.9	100.0

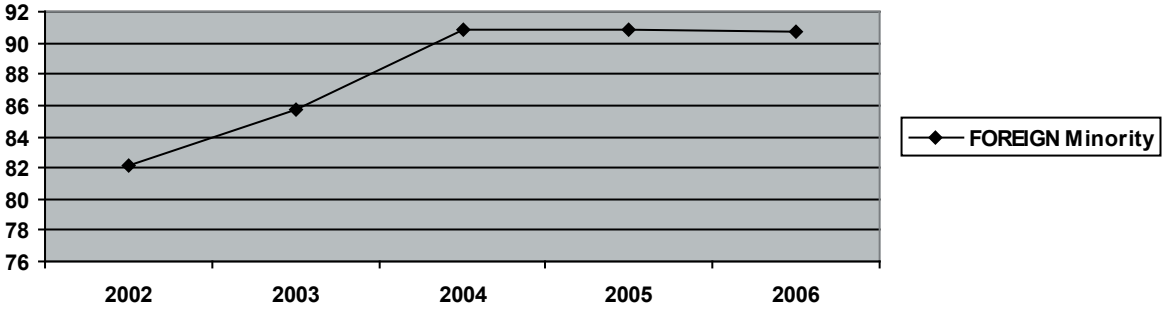
GRAPH 10F(1): NUMBER OF MINORITY PARTICIPANTS FOR FY 2002-2006



GRAPH 10F(2): PERCENTAGE COMPARISON OF DOMESTIC MINORITY ENROLLMENT TO TOTAL DOMESTIC ENROLLMENT FOR FY 2002-2006



GRAPH 10F(3): PERCENTAGE COMPARISON OF FOREIGN MINORITY ENROLLMENT TO TOTAL FOREIGN ENROLLMENT FOR FY 2002-2006



NOTE: Trend data vary over time because the data for each year represents the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported.

Comments on Table 10B:

1. The data reported in FY 2002 and later are from the new NIH population tracking system that was deployed with data reported in FY 2002 and later and allows separate reporting using the OLD form and the NEW form and separate reporting for Foreign and Domestic data.

Comments on Table 10C and 10D:

1. The NEW Form consists of Parts A and B for reporting years 2002-2006. This form is provided as part of the annual progress report.
2. Table 10C displays the NEW Form Part A for reporting separate race and ethnicity data.
3. Table 10D displays the NEW Form Part B, which is the distribution of Hispanics reported by race using the totals from the Hispanic or Latino column in Part A.

Comments on Table 10E:

1. The Total Enrollment, Total Domestic Enrollment, and Total Foreign Enrollment increases from FY 2002-2006.
2. The Domestic Enrollment decreased to approximately 80% while the Foreign enrollment increased to approximately 20%.
3. The vast majority of protocols are domestic protocols (approximately 94 to 96%) while Foreign protocols make up approximately 4% to 6% of total protocols.
4. Foreign enrollment was reported using the same race and ethnicity categories as domestic enrollment.

Comments on Table 10F:

1. Domestic Minority Enrollment has varied from 24.1% to 28.9% of Total Domestic Enrollment.
2. Foreign Minority Enrollment has varied from 82.2% to 90.9% of Total Foreign Enrollment.
3. The Total Minority Enrollment reported in FY 2006 was 52% Domestic and 48% Foreign (see Table 5). The small percentage of foreign protocols accounts for a significant proportion (48%) of the Total Minority Enrollment, as shown by comparing both domestic and foreign enrollment data.

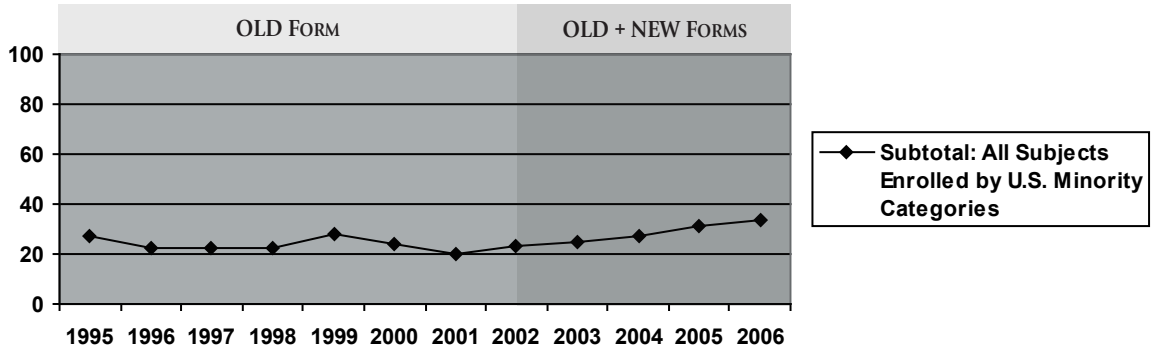
TABLE 11. Twelve Year Minority Trend Summary of the NIH Extramural and Intramural Phase III Clinical Research Reported in FY 1995-2006: Enrollment by Race and Ethnicity

TABLE 11A: PHASE III TWELVE YEAR SUMMARY TOTALS: ENROLLMENT BY SEX/GENDER IN ALL PROTOCOLS (OLD + NEW FORMS)

FY REPORTED/ FUNDED	FEMALES	MALES	UNKNOWN	ALL SUBJECTS*	SUBTOTAL BY MINORITY†	N PROTOCOLS‡
1995/1994	171,181	108,324	19,818	299,323	80,562	560
%	57.2	36.2	6.6	100.0	26.9	
1996/1995	264,755	203,698	21,210	489,663	110,669	608
%	54.1	41.6	4.3	100.0	22.6	
1997/1996	264,755	203,698	21,210	489,663	110,000	608
%	54.1	41.6	4.3	100.0	22.5	
1998/1997	228,417	74,389	2,705	305,511	69,599	320
%	74.8	24.3	0.9	100.0	22.8	
1999/1998	339,533	163,950	1,446	504,929	141,449	578
%	67.2	32.5	0.3	100.0	28.0	
2000/1999	313,952	180,705	1,086	495,743	120,339	589
%	63.3	36.5	0.2	100.0	24.3	
2001/2000	412,379	168,085	1,273	581,737	117,873	645
%	70.9	28.9	0.2	100.0	20.3	
2002/2001	278,876	195,090	781	474,747	111,269	754
%	58.7	41.1	0.2	100.0	23.4	
2003/2002	294,950	239,403	1,914	536,267	132,302	852
%	55.0	44.6	0.4	100.0	24.7	
2004/2003	301,353	242,913	1,101	545,367	150,456	573
%	55.3	44.5	0.2	100.0	27.6	
2005/2004	290,977	197,300	4,723	493,000	154,191	547
%	59.0	40.0	1.0	100.0	31.3	
2006/2005	314,066	179,975	5,389	499,430	167,446	624
%	62.9	36.0	1.1	100.0	33.5	

* The total of all subjects includes data from both OLD and NEW Forms.
† The subtotal of all subjects enrolled by U.S. minority categories
‡ Number of protocols with enrollment data from OLD and NEW Forms

GRAPH 11A(1): TOTAL PHASE III ENROLLMENT BY YEAR REPORTED



GRAPH 11A(2): SEX/GENDER PHASE III ENROLLMENT BY YEAR REPORTED

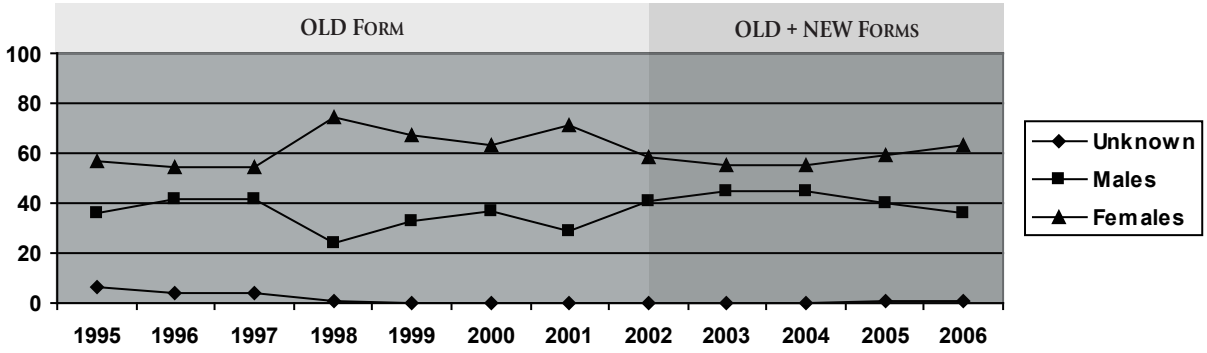


TABLE 11B: PHASE III OLD FORM: TOTAL OF ALL SUBJECTS REPORTED USING THE 1977 OMB STANDARDS IN A COMBINED RACE/ETHNICITY FORMAT

FY REPORTED/ FUNDED	AMERICAN INDIAN/ ALASKA NATIVE	ASIAN/ PACIFIC ISLANDER	BLACK OR AFRICAN AMERICAN	HISPANIC, NOT WHITE	WHITE	UNKNOWN OR OTHER	TOTAL	SUBTOTAL*	N PROTOCOLS†
1995/1994	5,358	2,740	52,433	20,031	172,773	45,988	299,323	80,562	560
%	1.8	0.9	17.5	6.7	57.7	15.4	100.0	26.9	
1996/1995	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608
%	0.9	8.2	9.6	4.0	65.6	11.8	100.0	22.6	
1997/1996	4,235	40,126	46,838	19,470	321,445	57,549	489,663	110,669	608
%	0.9	8.2	9.6	4.0	65.6	11.8	100.0	22.6	
1998/1997	5,030	5,324	42,805	16,440	229,534	6,378	305,511	69,599	320
%	1.6	1.7	14.0	5.4	75.1	2.1	100.0	22.8	
1999/1998	3,685	20,276	76,921	40,567	336,703	26,777	504,929	141,449	578
%	0.7	4.0	15.2	8.0	66.7	5.3	100.0	28.0	
2000/1999	3,726	24,017	62,512	30,084	335,824	39,580	495,743	120,339	589
%	0.8	4.8	12.6	6.1	67.7	8.0	100.0	24.3	
2001/2000	4,079	11,132	70,110	32,552	422,802	41,062	581,737	117,873	645
%	0.7	1.9	12.1	5.6	72.2	7.1	100.0	20.3	
2002/2001	1,645	20,560	51,991	29,636	315,543	12,228	431,603	103,832	660
%	0.4	4.8	12.0	6.9	73.1	2.8	100.0	24.1	
2003/2002	1,689	20,038	49,255	29,066	337,654	16,615	454,317	100,048	656
%	0.4	4.4	10.8	6.4	74.3	3.7	100.0	22.0	
2004/2003	1, 505	18,807	45,285	32,974	265,764	14,050	378,385	98,571	296
%	0.4	5.0	12.0	8.7	70.2	3.7	100.0	26.1	
2005/2004	1,319	17,740	39,402	21,829	231,492	4,507	316,289	80,290	210
%	0.4	5.6	12.5	6.9	73.2	1.4	100.0	25.4	
2006/2005	1,012	16,800	20,355	9,524	175,724	6,348	229,763	47,691	215
%	0.4	7.3	8.9	4.1	76.5	2.8	100.0	20.8	

* The subtotal is calculated using the U.S. minority categories OLD form.
† The number of protocols is based on protocols with enrollment data (OLD form).
See Notes and Comments below.

Table 11C: Phase III New Form: Total of All Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity

11C(1): Total of All Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total
2002/2001	159	799	4,647	52	34,654	560	2,273	43,144
%	0.4	1.9	10.8	0.1	80.3	1.3	5.3	100.0
2003/2002	484	2,609	21,641	220	47,869	989	8,138	81,950
%	0.6	3.2	26.4	0.3	58.4	1.2	9.9	100.0
2004/2003	1,396	4,385	43,721	611	106,793	4,419	5,657	166,982
%	0.8	2.6	26.2	0.4	64.0	2.6	3.4	100.0
2005/2004	2,164	9,192	50,338	462	101,238	3,063	10,254	176,711
%	1.2	5.2	28.5	0.3	57.3	1.7	5.8	100.0
2006/2005	4,630	32,360	50,780	535	126,670	4,246	50,446	269,667
%	1.7	12.0	18.8	0.2	47.0	1.6	18.7	100.0

11C(2): Total of All Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total
2002/2001	36,224	1,629	5,291	43,144
%	83.9	3.8	12.3	100.0
2003/2002	64,295	7,831	9,824	81,950
%	78.5	9.6	12.0	100.0
2004/2003	145,742	13,435	7,805	166,982
%	87.3	8.0	4.7	100.0
2005/2004	156,650	10,397	9,664	176,711
%	88.6	5.9	5.5	100.0
2006/2005	202,358	31,034	36,275	269,677
%	75.0	11.5	13.5	100.0

See Notes and Comments below.

Table 11D: Phase III Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Other	Total Hispanic or Latino	Subtotal Minority NEW Form	N Protocol*
2002/2001	49	22	31	4	660	304	560	1,630	7,437	94
%	3.0	1.3	1.9	0.2	40.5	18.7	34.4	100.0	17.2	
2003/2002	37	70	186	23	2,115	203	5,197	7,831	32,254	196
%	0.5	0.9	2.4	0.3	27.0	2.6	66.4	100.0	39.4	
2004/2003	269	59	193	26	7,264	3,052	2,572	13,435	54,405	277
%	2.0	0.4	1.4	0.2	54.1	22.7	19.1	100.0	32.6	
2005/2004	759	42	446	45	3,667	423	5,015	10,397	73,901	337
%	7.3	0.4	4.3	0.4	35.3	4.1	48.2	100.0	41.8	
2006/2005	2,307	50	720	40	6,872	713	20,332	31,034	119,755	409
%	7.4	0.2	2.3	0.1	22.1	2.3	65.5	100.0	44.4	

*This includes the number of protocols with enrollment data (NEW Form).

TABLE 11E: COMPARISON OF DOMESTIC AND FOREIGN PHASE III ENROLLMENT AND PROTOCOLS WITH ENROLLMENT FOR THE PERIOD FY 2002-2006

11E(1): ENROLLMENT

FY REPORTED/ FUNDED	TOTAL ENROLLMENT*	TOTAL DOMESTIC ENROLLMENT	PERCENT DOMESTIC ENROLLMENT	TOTAL FOREIGN ENROLLMENT	PERCENT FOREIGN ENROLLMENT
2002/2001	474,747	444,436	93.6	30,311	6.4
2003/2002	536,267	486,857	90.8	49,410	9.2
2004/2003	545,367	496,241	91.0	49,126	9.0
2005/2004	493,000	437,902	88.8	55,098	11.2
2006/2005	499,430	400,297	80.2	99,133	19.8

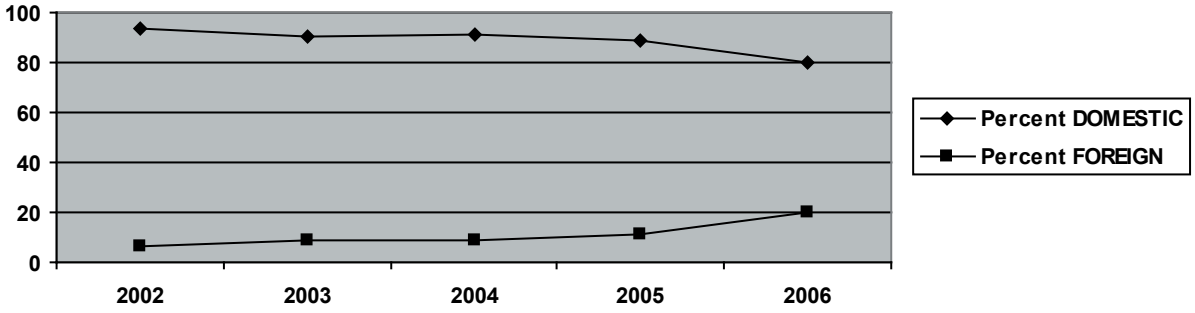
* Total enrollment includes OLD + NEW Forms.

11E(2): PROTOCOLS

FY REPORTED/ FUNDED	TOTAL PROTOCOLS W/ ENROLLMENT*	TOTAL DOMESTIC PROTOCOLS	PERCENT DOMESTIC PROTOCOLS	TOTAL FOREIGN PROTOCOLS	PERCENT FOREIGN PROTOCOLS
2002/2001	754	582	77.2	172	22.8
2003/2002	852	643	75.5	209	24.5
2004/2003	573	549	95.8	24	4.2
2005/2004	547	517	94.5	30	5.5
2006/2005	624	564	90.4	60	9.6

* Number of protocols with enrollment data from OLD + NEW Forms.

GRAPH 11E(1): PERCENTAGE OF PHASE III DOMESTIC AND FOREIGN ENROLLMENT



GRAPH 11E(2): NUMBER OF PHASE III DOMESTIC AND FOREIGN PROTOCOLS

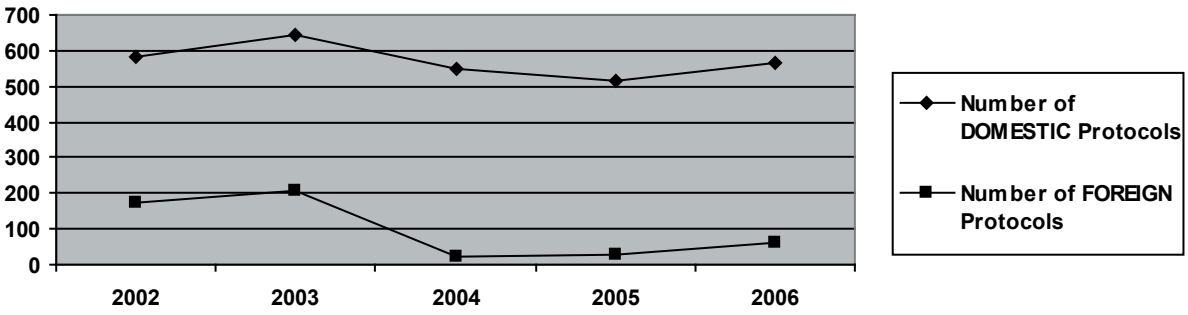
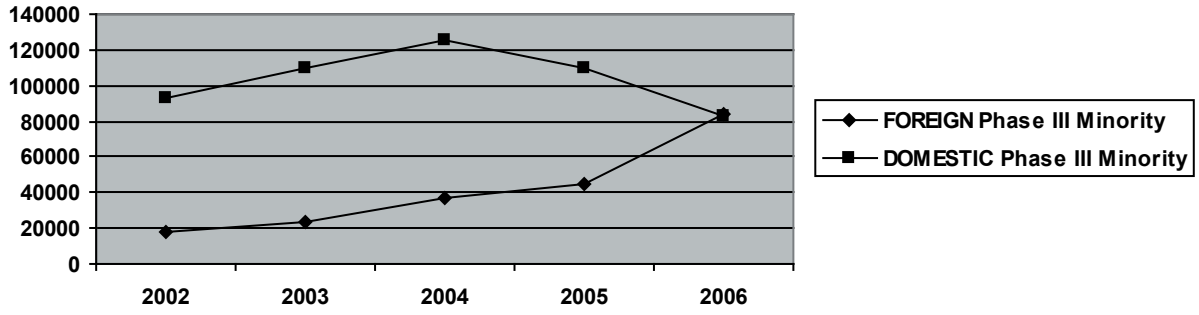


Table 11F: Phase III Foreign and Domestic Minority Comparison for FY 2002-2006

FY Reported/ Funded	Foreign Phase III Minority	Foreign Phase III Total	Domestic Phase III Minority	Domestic Phase III Total
2002/2001	18,308	30,311	92,961	444,436
%	60.4	100.0	20.9	100.0
2003/2002	23,927	49,410	109,376	486,857
%	48.4	100.0	22.5	100.0
2004/2003	37,126	49,126	125,813	496,241
%	75.6	100.0	25.4	100.0
2005/2004	44,281	55,098	109,910	437,902
%	80.4	100.0	25.1	100.0
2006/2005	84,412	99,133	83,034	400,297
%	85.2	100.0	20.7	100.0

Graph 11F: Number of Minority Participants in Phase III Clinical Studies for FY 2002-2006



NOTE: Trend data vary over time because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported. Data from Tables 11B, 11C, and 11D are combined to provide summary data in Table 11A.

Comments on Table 11A:

1. Table 11A summarizes enrollment by sex/gender and minority race/ethnicity categories for the twelve year reporting period (1995-2006). The data are compiled from Tables 11B, 11C, and 11D, which provide the detailed distributions by sex/gender and race/ethnicity using the OLD Form for enrollment (11B) and the NEW Form for enrollment (Tables 11C and 11D).
2. The Race and Ethnicity data in the OLD Form and the NEW Form cannot be combined by individual race and ethnicity categories because the categories reflect the different OMB formats used based in the 1977 OMB standards (OLD Form) and the 1997 OMB standards (NEW Form).

Comments on Tables 11C and D:

1. The NEW Form consists of Parts A and B (Tables 11C and 11D) for reporting years 2002-2006. This form is provided as part of the annual progress report.
2. Table 11C displays the NEW Form Part A for reporting separate race and ethnicity data.
3. Table 11D displays the NEW Form Part B, which is the distribution of Hispanics reported by race, using the totals from the Hispanic or Latino column in Part A.

Comments on Table 11E:

1. The Total Enrollment, Total Domestic Enrollment, and Total Foreign Enrollment increase from FY 2002-2006.
2. The Domestic Enrollment decreased to approximately 80% ,while the Foreign Enrollment increased to approximately 20%.
3. The vast majority of protocols in FY 2004-2006 are Domestic protocols (approximately 90.4%–95.8%), while Foreign protocols make up approximately 4.2%-9.6% of total protocols
4. Foreign enrollment was reported using the same race and ethnicity categories as Domestic enrollment.

Comments on Table 11F:

1. Domestic Minority Enrollment has varied from 24.1 to 28.9% of Total Domestic Enrollment.
2. Foreign Minority Enrollment has varied from 82.2 to 90.9% of Total Foreign Enrollment, reflecting that most of the Foreign research is done in countries that are within the OMB race and ethnicity origin categories that are included in the summary minority data used in this report.
3. The Total Minority Enrollment reported in FY 2006 was 52% Domestic and 48% Foreign (see Table 5). The small percentage of Foreign protocols account for a significant proportion (48%) of the Total Minority Enrollment, as shown by comparing both Domestic and Foreign enrollment data.

Table 12. Domestic Protocols: Summary of NIH Extramural and Intramural Clinical Research Reported: FY 2002-2006: Enrollment Using U.S. Race/Ethnicity Categories

TABLE 12A: FIVE YEAR SUMMARY TOTALS: DOMESTIC SUBJECTS IN DOMESTIC PROTOCOLS (OLD AND NEW FORMS)

FY REPORTED/ FUNDED	FEMALES	MALES	UNKNOWN	TOTAL DOMESTIC SUBJECTS*	SUBTOTAL BY MINORITY CATEGORIES†	N DOMESTIC PROTOCOLS‡
2002/2001	6,583,087	3,506,787	59,995	10,149,869	2,754,820	8,425
%	64.9	34.6	0.6	100.0	27.1	
2003/2002	7,392,404	4,393,496	125,457	11,911,357	2,935,363	9,578
%	62.1	36.9	1.1	100.0	24.6	
2004/2003	8,881,299	5,199,765	278,729	14,358,793	3,464,356	9,760
%	61.8	36.2	1.9	100.0	24.1	
2005/2004	7,887,209	4,515,242	267,407	12,669,858	3,468,864	9,862
%	62.3	35.6	2.1	100.0	27.4	
2006/2005	7,684,453	3,566,577	174,671	11,425,701	3,301,135	10,294
%	67.3	31.2	1.5	100.0	28.9	

* Total Domestic subjects (OLD and NEW Forms)

† Subtotal of Domestic subjects enrolled by U.S. minority categories

‡ Number of Domestic Protocols with Enrollment data (OLD and NEW Forms)

TABLE 12B: OLD FORM: TOTAL OF ALL DOMESTIC SUBJECTS REPORTED USING THE 1977 OMB STANDARDS IN A COMBINED RACE/ETHNICITY FORMAT

FY REPORTED/ FUNDED	AMERICAN INDIAN/ ALASKA NATIVE	ASIAN/ PACIFIC ISLAND-ER	BLACK OR AFRICAN AMERICAN	HISPANIC, NOT WHITE	WHITE	UNKNOWN OR OTHER	TOTAL DOMESTIC SUBJECTS*	DOMESTIC SUBTOTAL MINORITY SUBJECTS†	N DOMESTIC PROTOCOLS‡
2002/2001	45,639	752,203	673,726	378,300	3,880,431	316,053	6,046,352	1,849,868	5,783
%	0.8	12.4	11.1	6.3	64.2	5.2	100.0	30.6	
2003/2002	36,238	249,420	455,329	264,336	3,100,815	266,339	4,372,477	1,005,323	4,478
%	0.8	5.7	10.4	6.0	70.9	6.1	100.0	23.0	
2004/2003	28,953	196,647	322,078	194,762	2,273,619	157,464	3,173,523	742,440	2,702
%	0.9	6.2	10.1	6.1	71.6	5.0	100.0	23.4	
2005/2004	22,375	89,119	210,465	126,351	1,245,337	93,239	1,786,886	448,310	1,736
%	1.3	5.0	11.8	7.1	69.7	5.2	100.0	25.1	
2006/2005	19,628	51,701	148,224	74,312	866,683	61,480	1,222,028	293,865	1,361
%	1.6	4.2	12.1	6.1	70.9	5.0	100.0	24.0	

* Total Domestic Enrollment (OLD Form)

† The subtotal of Domestic subjects is calculated using the U.S. minority categories OLD form.

‡ The number of protocols is based on protocols with enrollment data (OLD form).
See Notes and Comments below.

Table 12C: NEW Form Part A: Inclusion Enrollment Report (Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats): Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

12C(1): Total of All Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total by Race*
2002/2001	74,593	174,215	473,699	7,623	2,626,547	30,200	716,640	4,103,517
%	1.8	4.2	11.5	0.2	64.0	0.7	17.5	100.0
2003/2002	61,526	295,061	897,518	23,068	5,161,965	94,138	1,005,604	7,538,880
%	0.8	3.9	11.9	0.3	68.5	1.2	13.3	100.0
2004/2003	97,854	485,137	1,280,129	42,945	7,772,927	172,185	1,335,093	11,186,270
%	0.9	4.3	11.4	0.4	69.5	1.5	11.9	100.0
2005/2004	291,044	655,959	1,232,957	42,993	7,485,193	164,096	1,010,730	10,882,972
%	2.7	6.0	11.3	0.4	68.8	1.5	9.3	100.0
2006/2005	111,048	946,613	1,032,199	35,142	6,844,960	178,275	1,055,436	10,203,673
%	1.1	9.3	10.1	0.3	67.1	1.7	10.3	100.0

* Total of all subjects by racial categories (NEW Form)

12C(2): Total of All Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total by Ethnicity*
2002/2001	2,785,590	285,921	1,032,006	4,103,517
%	67.9	7.0	25.1	100.0
2003/2002	6,003,326	602,018	933,536	7,538,880
%	79.6	8.0	12.4	100.0
2004/2003	8,893,158	720,551	1,572,561	11,186,270
%	79.5	6.4	14.1	100.0
2005/2004	9,120,293	721,138	1,041,541	10,882,972
%	83.8	6.6	9.6	100.0
2006/2005	8,384,360	796,556	1,022,757	10,203,673
%	82.2	7.8	10.0	100.0

See Notes and Comments below.

* Total of all subjects by ethnic category

12D: NEW FORM PART B: HISPANIC ENROLLMENT REPORT: NUMBER OF HISPANICS OR LATINOS ENROLLED TO DATE (CUMULATIVE)

FY REPORTED/ FUNDED	AMERICAN INDIAN/ ALASKA NATIVE	ASIAN	BLACK OR AFRICAN AMERICAN	HAWAIIAN/ PACIFIC ISLANDER	WHITE	MORE THAN ONE RACE	UNKNOWN OR NOT REPORTED	TOTAL HISPANIC OR LATINO*	SUBTOTAL DOMESTIC MINORITY†	N DOMESTIC PROTOCOL‡
2002/2001	1,163	436	12,005	98	69,313	5,626	75,309	163,950	904,952	2,642
%	0.7	0.3	7.3	0.1	42.3	3.4	45.9	100.0	22.1	
2003/2002	3,756	1,950	13,345	678	349,844	23,560	208,885	602,018	1,930,040	5,100
%	0.6	0.3	2.2	0.1	58.1	3.9	34.7	100.0	25.6	
2004/2003	6,293	5,026	12,498	2,037	356,575	51,031	287,091	720,551	2,721,916	7,058
%	0.9	0.7	1.7	0.3	49.5	7.1	39.8	100.0	24.3	
2005/2004	22,057	7,810	19,282	1,981	362,707	36,503	270,798	721,138	3,020,554	8,126
%	3.1	1.1	2.7	0.3	50.3	5.1	37.6	100.0	27.8	
2006/2005	15,498	6,540	19,870	1,505	374,830	49,150	329,163	796,556	3,007,270	8,933
%	1.9	0.8	2.5	0.2	47.1	6.2	41.3	100.0	29.5	

* Total Hispanic or Latinos by racial categories

† Domestic subtotal using U.S. minority categories (NEW Form Parts A and B)

‡ This includes the number of protocols with enrollment data (NEW Form).

NOTES on Table 12: Data from Tables 12B, 12C, and 12D are combined to provide summary data in Table 12A.

FY 2002 Reported Data:

One Domestic study had an enrollment of 540,833 subjects (OLD Form).
One Domestic study had an enrollment of 1,571,305 subjects (OLD Form).

FY 2003 Reported Data:

One Domestic study had an enrollment of 800,000 subjects (NEW Form).
One Domestic study had an enrollment of 1,389,920 subjects (NEW Form).
One Domestic study had an enrollment of 1,799,820 subjects (NEW Form).

FY 2004 Reported Data:

One Domestic study had an enrollment of 540,833 subjects (NEW Form).
One Domestic study had an enrollment of 800,000 subjects (NEW Form).
One Domestic study had an enrollment of 1,138,302 subjects (NEW Form).
One Domestic study had an enrollment of 1,419,475 subjects (NEW Form).
One Domestic study had an enrollment of 1,799,820 subjects (NEW Form).

FY 2005 Reported Data:

One Domestic study had an enrollment of 540,833 subjects (NEW Form).
One Domestic study had an enrollment of 800,000 subjects (NEW Form).
One Domestic study had an enrollment of 1,595,620 subjects (NEW Form).
One Domestic study had an enrollment of 1,799,820 subjects (NEW Form).

FY 2006 Reported Data:

One Domestic study had an enrollment of 875,010 subjects (NEW Form).

One Domestic study had an enrollment of 1,964,668 subjects (NEW Form).
One Domestic study had an enrollment of 540,833 subjects (NEW Form).

Comments on Table 12A:

1. There were approximately an average of 63% females, 35% males, and 2% unknown sex enrolled in Domestic protocols from 2002-2006.
2. There was approximately an average of 27% Domestic minority subjects enrolled in Domestic protocols from 2002-2006.
3. Total Domestic enrollment ranged from 10.1 million to 11.5 million during these 5 years.
4. The number of Domestic protocols increased from 8,425 to 10,294 in 2006.

Table 13. Domestic Protocols: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY 2002-2006: Enrollment Using U.S. Race/Ethnicity Categories

Table 13A: Phase III Five Year Summary Totals: Domestic Subjects in Domestic Protocols (OLD and NEW Forms)

FY Reported/ Funded	Females	Males	Unknown	Total Domestic Subjects*	Subtotal by Minority Categories†	N Domestic Protocols‡
2002/2001	264,517	179,179	740	444,436	92,961	582
%	59.5	40.3	0.2	100.0	20.9	
2003/2002	266,913	218,166	1,778	486,857	109,376	643
%	54.8	44.8	0.4	100.0	22.5	
2004/2003	277,333	217,890	1,018	496,241	125,813	549
%	55.9	43.9	0.2	100.0	25.4	
2005/2004	261,589	174,137	2,176	437,902	109,910	517
%	59.7	39.8	0.5	100.0	25.1	
2006/2005	258,467	137,621	4,209	400,297	83,034	564
%	64.6	34.4	1.1	100.0	20.7	

* Total Domestic subjects (OLD and NEW Forms)
† Subtotal of Domestic subjects enrolled by U.S. minority categories
‡ Number of Domestic Protocols with Enrollment data (OLD and NEW Forms)

Table 13B: OLD Form: Total of All Domestic Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported/ Funded	American Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown or Other	Total Domestic Enroll-ment*	Domestic Subtotal Minority†	N Domestic Protocols‡
2002/2001	1,586	8,291	49,184	27,912	305,964	10,670	403,607	86,973	494
%	0.4	2.1	12.2	6.9	75.8	2.6	100.0	21.5	
2003/2002	1,612	7,610	48,975	25,567	322,600	8,538	414,902	83,764	468
%	0.4	1.8	11.8	6.2	77.8	2.1	100.0	20.2	
2004/2003	1,504	6,739	45,233	31,967	262,671	6,447	354,561	85,443	286
%	0.4	1.9	12.8	9.0	74.1	1.8	100.0	24.1	
2005/2004	1,319	5,488	39,401	20,646	229,235	4,493	300,582	66,854	205
%	0.4	1.8	13.1	6.9	76.3	1.5	100.0	22.2	
2006/2005	996	4,505	20,325	9,512	171,191	5,673	212,202	35,338	207
%	0.5	2.1	9.6	4.5	80.7	2.7	100.0	16.7	

* Total Domestic Enrollment (OLD Form)
† Domestic Subtotal using U.S. minority categories (OLD form) The subtotal of Domestic subjects is calculated using the U.S. minority categories OLD form.
‡ Number of Domestic protocols with enrollment data (OLD form)
See Notes and Comments below.

Table 13C: NEW Form Part A: Inclusion Enrollment Report (Total of All Domestic Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats). Part A: Total Enrollment Report: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

13C(1): Total Enrollment Report of All Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total Subjects by Race*
2002/2001	159	798	3,199	52	34,541	560	1,520	40,829
%	0.4	2.0	7.8	0.1	84.6	1.4	3.7	100.0
2003/2002	477	2,586	14,031	220	46,774	989	6,878	71,955
%	0.7	3.6	19.5	0.3	65.0	1.4	9.6	100.0
2004/2003	1,396	4,373	22,307	611	106,260	1,849	4,884	141,680
%	1.0	3.1	15.7	0.4	75.0	1.3	3.4	100.0
2005/2004	1,775	4,920	24,390	462	93,662	3,063	9,048	137,320
%	1.3	3.6	17.8	0.3	68.2	2.2	6.6	100.0
2006/2005	2,724	5,312	23,267	530	118,577	4,077	33,608	188,095
%	1.4	2.8	12.4	0.3	63.0	2.2	17.9	100.0

* Total of all subjects by racial categories (NEW Form)

13C(2): Total of All Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total Subjects by Ethnicity
2002/2001	34,662	1,629	4,538	40,828
%	84.9	4.0	11.1	100.0
2003/2002	55,575	7,828	8,552	71,955
%	77.2	10.9	11.9	100.0
2004/2003	123,770	10,863	7,047	141,680
%	87.4	7.7	5.0	100.0
2005/2004	118,528	9,773	9,019	137,320
%	86.3	7.1	6.6	100.0
2006/2005	141,688	13,550	32,857	188,095
%	75.3	7.2	17.5	100.0

See Notes and Comments below.

Table 13D: NEW Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total Hispanic or Latino*	Subtotal Domestic Minority†	N Domestic Protocols‡
2002/2001	49	21	31	4	660	304	560	1,629	5,988	88
%	3.0	1.3	1.9	0.2	40.5	18.7	34.4	100.0	14.7	
2003/2002	37	70	186	23	2,113	203	5,196	7,828	25,612	175
%	0.5	0.9	2.4	0.3	27.0	2.6	66.4	100.0	35.6	
2004/2003	269	59	193	26	7,262	482	2,572	10,863	40,370	263
%	2.5	0.5	1.8	0.2	66.9	4.4	23.7	100.0	28.5	
2005/2004	371	42	446	45	3,663	423	4,783	9,773	43,056	312
%	3.8	0.4	4.6	0.5	37.5	4.3	48.9	100.0	31.4	
2006/2005	458	47	507	40	5,544	712	6,242	13,550	47,696	357
%	3.4	0.3	3.7	0.3	40.9	5.3	46.1	100.0	25.4	

* Total Hispanic or Latinos by racial categories
† Domestic subtotal using U.S. minority categories (NEW Form Parts A and B)
‡ Number of Domestic protocols with enrollment data (NEW Form)

NOTE: Data from Tables 13B, 13C, and 13D are combined to provide the summary data in Table 13A.

Comments on Table 13A:

1. There was approximately an average of 57% females, 42% males, and 0.3% of unknown sex enrolled in Domestic protocols from 2002-2005.
2. There was approximately an average of 23.5% Domestic minority subjects enrolled in Domestic Phase III protocols from 2002-2006.
3. Total Domestic Phase III enrollment ranged from 400,297 to 496,241 during these 5 years.
4. The number of Domestic Phase III protocols ranged from 517 to 564 in 2006.

Table 14. Foreign Protocols: Summary of NIH Extramural and Intramural Clinical Research Reported in FY 2002-2006: Enrollment Using U.S. Race/Ethnicity Categories

Table 14A: Five Year Summary Totals: Foreign Subjects in Clinical Research Foreign Protocols (OLD and NEW Forms)

FY Reported/ Funded	Females	Males	Unknown	Total Foreign Subjects*	Subtotal by Minority Categories†	N Foreign Protocols‡
2002/2001	553,056	379,294	13,833	946,083	777,461	482
%	58.5	40.1	1.5	100.0	82.2	
2003/2002	1,122,077	1,728,000	10,820	2,860,897	2,452,329	638
%	39.2	60.4	0.4	100.0	85.7	
2004/2003	2,007,798	2,542,127	14,202	4,564,127	4,147,255	365
%	44.0	55.7	0.3	100.0	90.9	
2005/2004	1,616,713	1,426,665	9,516	3,052,894	2,776,565	371
%	53.0	46.7	0.3	100.0	90.9	
2006/2005	1,788,820	1,605,628	10,781	3,405,229	3,087,181	464
%	52.5	47.2	0.3	100.0	90.7	

* Total Foreign subjects (OLD and NEW Forms)
† Subtotal of Foreign subjects enrolled by U.S. minority categories
‡ Number of Foreign Protocols with Enrollment data (OLD and NEW Forms)

Table 14B: OLD Form: Total of All Foreign Subjects Reported Using the 1977 OMB Standards in a Combined Race/Ethnicity Format

FY Reported/ Funded	America Indian/ Alaska Native	Asian/ Pacific Islander	Black or African American	Hispanic, Not White	White	Unknown or Other	Total Foreign Enrollment*	Foreign Subtotal by Minority†	N Foreign Protocols‡
2002/2001	69	468,958	21,407	19,075	143,768	3,565	656,842	509,509	380
%	0.0	71.4	3.3	2.9	21.9	0.5	100.0	77.6	
2003/2002	341	481,122	17,097	24,187	137,469	12,562	672,778	522,747	425
%	0.1	71.5	2.5	3.6	20.4	1.9	100.0	77.7	
2004/2003	434	110,405	20,110	19,560	74,910	14,666	240,085	150,509	80
%	0.2	46.0	8.4	8.1	31.2	6.1	100.0	62.7	
2005/2004	0	165,479	19,150	8,621	21,752	9,166	224,168	193,250	50
%	0.0	73.8	8.5	3.8	9.7	4.1	100.0	86.2	
2006/2005	20	80,085	724	4,284	16,358	1,751	103,222	85,113	30
%	0.0	77.6	0.7	4.2	15.8	1.7	100.0	82.5	

*Total Foreign Enrollment (OLD Form)
† Foreign subtotal using U.S. Minority Categories (OLD Form)
‡ The number of Foreign protocols is based on protocols with enrollment data (OLD form).
See Notes and Comments below.

Table 14C: NEW Form Part A: Inclusion Enrollment Report (Total of all Foreign Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats: Part A: Total Enrollment Report: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

14C(1): Total of All Foreign Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total Subjects by Race*
2002/2001	3,271	180,022	68,071	14,013	19,970	741	3,153	289,241
%	1.1	62.2	23.5	4.8	6.9	0.3	1.1	100.0
2003/2002	2,018	1,842,941	62,572	14,501	253,745	5,324	7,018	2,188,119
%	0.1	84.2	2.9	0.7	11.6	0.2	0.3	100.0
2004/2003	193	3,860,259	99,728	11,507	292,142	14,056	46,157	4,324,042
%	0.0	89.3	2.3	0.3	6.8	0.3	1.1	100.0
2005/2004	1,171	2,390,404	125,305	10,293	187,697	18,857	94,999	2,828,726
%	0.0	84.5	4.4	0.4	6.6	0.7	3.4	100.0
2006/2005	30,519	2,516,589	219,140	3,318	244,057	143,279	145,105	3,302,007
%	0.9	76.2	6.6	0.1	7.4	4.3	4.4	100.0

* Total of all subjects by racial categories (NEW Form)

14C(2): Total of All Foreign Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total Subjects by Ethnicity*
2002/2001	278,618	6,064	4,559	289,241
%	96.3	2.1	1.6	100.0
2003/2002	2,158,933	9,623	19,563	2,188,119
%	98.7	0.4	0.9	100.0
2004/2003	4,275,684	35,788	12,570	4,324,042
%	98.9	0.8	0.3	100.0
2005/2004	2,683,871	52,801	92,054	2,828,726
%	94.9	1.9	3.3	100.0
2006/2005	2,923,885	257,756	120,366	3,302,007
%	88.5	7.8	3.6	100.0

See Notes and Comments below.
* Total of all subjects by ethnic category

Table 14D: NEW Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total Hispanic or Latino*	Foreign Subtotal Minority†	N Foreign Protocol*
2002/2001	1,461	0	4	0	1,659	683	175	3,982	267,952	102
%	36.7	0.0	0.1	0.0	41.7	17.2	4.4	100.0	92.6	
2003/2002	1,644	3	1,222	0	632	4,528	1,594	9,623	1,929,582	213
%	17.1	0.0	12.7	0.0	6.6	47.1	16.6	100.0	88.2	
2004/2003	115	14	12,778	0	4,537	11,878	6,466	35,788	3,996,746	285
%	0.3	0.0	35.7	0.0	12.7	33.2	18.1	100.0	92.4	
2005/2004	682	6	164	0	26,161	14,664	11,124	52,801	2,583,315	321
%	1.3	0.0	0.3	0.0	49.5	27.8	21.1	100.0	91.3	
2006/2005	29,576	101	1,842	688	42,665	136,326	46,558	257,756	3,002,068	434
%	11.5	0.0	0.7	0.3	16.6	52.9	18.1	100.0	90.9	

* Total Foreign Hispanic or Latino subjects by racial categories
† Foreign subtotal using U.S. minority categories (NEW Form Parts A and B)
‡ This includes the number of Foreign protocols with enrollment data (NEW Form).

NOTES on Table 14: Data from Tables 14B, 14C, and 14D are combined to provide the summary data in Table 14A.

FY 2002 Reported Data:
One study in Vietnam had an enrollment of 302,381 subjects (OLD Form).

FY 2003 Reported Data:
One study in Vietnam had an enrollment of 302,381 subjects (OLD Form).
One study in China had an enrollment of 1,910,000 subjects (NEW Form).

FY 2004 Reported Data:
One study in China had an enrollment of 1,910,000 subjects (NEW Form).
One study in India had an enrollment of 2,000,000 subjects (NEW Form).

FY 2005 Reported Data:
One study in India had an enrollment of 2,200,000 subjects (NEW Form).

FY 2006 Reported Data:
One study in India had an enrollment of 2,200,000 subjects (NEW Form).

Comments on Table 14A:

1. The percent of females varied from 39.2% to 58.5% in Foreign protocols from 2002-2005. The percent of males varied from 40.1% to 60.4%.
2. The percent of Foreign subjects enrolled by U.S. minority categories in Foreign protocols increased from 82.2% to 90.9% from 2002 to 2005.
3. Total Foreign enrollment ranged from 777,461 to 4.15 million during these 5 years.
4. The number of Foreign protocols ranged from 638 in 2003 to 317 in 2005.

TABLE 15. Foreign Protocols: Summary of NIH Extramural and Intramural Phase III Clinical Research Reported in FY 2002-2006: Enrollment Using U.S. Race/Ethnicity Categories

TABLE 15A: PART A: PHASE III FIVE YEAR SUMMARY TOTALS: FOREIGN SUBJECTS IN FOREIGN PROTOCOLS (OLD AND NEW FORMS)

FY REPORTED/ FUNDED	FEMALES	MALES	UNKNOWN	TOTAL FOREIGN SUBJECTS*	SUBTOTAL BY MINORITY CATEGORIES†	N FOREIGN PROTOCOLS‡
2002/2001	14,359	15,911	41	30,311	18,308	172
%	47.4	52.5	0.1	100.0	60.4	
2003/2002	28,037	21,237	136	49,410	23,927	209
%	56.7	43.0	0.3	100.0	48.4	
2004/2003	24,020	25,023	83	49,126	37,126	24
%	48.9	50.9	0.2	100.0	75.6	
2005/2004	29,388	23,163	2,547	55,098	44,281	30
%	53.3	42.0	4.6	100.0	80.4	
2006/2005	55,599	42,354	1,180	99,133	84,412	60
%	56.1	42.7	1.2	100.0	85.2	

* Total Foreign subjects (OLD and NEW Forms)
† Subtotal of Foreign subjects enrolled by U.S. minority categories
‡ Number of Foreign Protocols with Enrollment data (OLD and NEW Forms)

TABLE 15B: OLD FORM: TOTAL OF ALL FOREIGN SUBJECTS REPORTED USING THE 1977 OMB STANDARDS IN A COMBINED RACE/ETHNICITY FORMAT

FY REPORTED/ FUNDED	AMERICAN INDIAN/ ALASKA NATIVE	ASIAN/ PACIFIC ISLANDER	BLACK OR AFRICAN AMERICAN	HISPANIC, NOT WHITE	WHITE	UNKNOWN OR OTHER	TOTAL FOREIGN ENROLLMENT*	FOREIGN SUBTOTAL†	N FOREIGN PROTOCOLS‡
2002/2001	59	12,269	2,807	1,724	9,579	1,558	27,996	16,859	166
%	0.2	43.8	10.0	6.2	34.2	5.6	100.0	60.2	
2003/2002	77	12,428	280	3,499	15,054	8,077	39,415	16,284	188
%	0.2	31.5	0.7	8.9	38.2	20.5	100.0	41.3	
2004/2003	1	12,068	52	1,007	3,093	7,603	23,824	13,128	10
%	0.0	50.7	0.2	4.2	13.0	31.9	100.0	55.1	
2005/2004	0	12,252	1	1,183	2,257	14	15,707	13,436	5
%	0.0	78.0	0.0	7.5	14.4	0.1	100.0	85.5	
2006/2005	16	12,295	30	12	4,533	675	17,561	12,353	8
%	0.1	70.0	0.2	0.1	25.8	3.8	100.0	70.3	

* Total Foreign enrollment (OLD Form)
† The subtotal of Foreign subjects is calculated using the U.S. minority categories OLD form.
‡ The number of Foreign protocols is based on protocols with enrollment data (OLD form).
See Notes and Comments below.

Table 15C: NEW Form Part A: Inclusion Enrollment Report (Total of All Foreign Subjects Reported Using the 1997 OMB Standards for Separate Race and Ethnicity Formats): Total Enrollment Report: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

15C(1): Total of Subjects by Race

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Total Foreign Subjects*
2002/2001	0	1	1,448	0	113	0	753	2,315
%	0.0	0.0	62.5	0.0	4.9	0.0	32.5	100.0
2003/2002	7	23	7,610	0	1,095	0	1,260	9,995
%	0.1	0.2	76.1	0.0	11.0	0.0	12.6	100.0
2004/2003	0	12	21,414	0	553	2,570	753	25,302
%	0.0	0.0	84.6	0.0	2.2	10.2	3.0	100.0
2005/2004	389	4,272	25,948	0	7,576	0	1,206	39,391
%	1.0	10.8	65.9	0.0	19.2	0.0	3.1	100.0
2006/2005	1,906	27,048	27,513	5	8,093	169	26,838	91,572
%	2.1	29.5	30.0	0.0	8.8	0.2	29.3	100.0

* Total of all subjects in all racial categories (NEW Form)

15C(2): Total of Subjects by Ethnicity

FY Reported/ Funded	Not Hispanic	Hispanic or Latino	Unknown/ Not Reported	Total Foreign Subjects*
2002/2001	1,562	0	753	2,315
%	67.5	0.0	32.5	100.0
2003/2002	8,720	3	1,272	9,995
%	87.2	0.0	12.7	100.0
2004/2003	21,972	2,572	758	25,300
%	86.8	10.2	3.0	100.0
2005/2004	38,122	624	645	39,391
%	96.8	1.6	1.6	100.0
2006/2005	60,670	17,484	3,418	81,572
%	74.4	21.4	4.2	100.0

See Notes and Comments below.

* Total of all Foreign subjects by ethnic category

15D: New Form Part B: Hispanic Enrollment Report: Number of Hispanics or Latinos Enrolled to Date

FY Reported/ Funded	American Indian/ Alaska Native	Asian	Black or African American	Hawaiian/ Pacific Islander	White	More Than One Race	Unknown or Not Reported	Total Hispanic or Latino*	Foreign Subtotal Minority†	N Foreign Protocol‡
2002/2001	0	0	0	0	0	0	0	0	1,449	6
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	62.6	
2003/2002	0	0	0	0	2	0	1	3	7,643	21
%	0.0	0.0	0.0	0.0	66.7	0.0	33.3	100.0	76.5	
2004/2003	0	0	0	0	2	2,570	0	2,572	23,998	14
%	0.0	0.0	0.0	0.0	0.1	99.9	0.0	100.0	94.8	
2005/2004	388	0	0	0	4	0	232	624	30,845	25
%	62.2	0.0	0.0	0.0	0.6	0.0	37.2	100.0	78.3	
2006/2005	1,849	3	213	0	1,328	1	14,090	17,484	72,059	52
%	10.6	0.0	1.2	0.0	7.6	0.0	80.6	100.0	78.7	

* Total Foreign Hispanic or Latino subjects by racial categories
† Foreign subtotal using U.S. minority categories (NEW Form Parts A and B)
‡ This includes the number of Foreign protocols with enrollment data (NEW Form).
NOTE: Data from Tables 15B, 15C, and 15D are combined to provide the summary data in Table 15A.

Comments on Table 15A:

1. The percent females varied from 47.4% to 56.7% in Phase III Foreign protocols from 2002-2006. The percent of males varied from 42.0% to 52.7%.
2. The percent Foreign subjects enrolled by U.S. minority categories in Phase III Foreign protocols increased from 60.4% to 85.2% from 2002 to 2006.
3. Total Phase III Foreign enrollment increased from 30,311 to 99,133 during these five years.
4. The number of Phase III Foreign protocols dropped from 209 in 2003 to 60 in 2005.

ORWH CAREER DEVELOPMENT PROGRAMS

In addition to extramural career development supported through the BIRCWH program, which is described above, the ORWH supports a number of career development programs. The ORWH works with many valued partners to develop and promote initiatives to develop scientific career training to both extramural investigators and intramural postdoctoral scientists and fellows. These programs are for both men and women who wish to work on women's health and sex/gender research. The following is a description of activities related to career development that are supported by the ORWH and its collaborators, starting with key activities for the extramural community followed by those for intramural scientists.

Biomedical Careers

A major component of the ORWH mandate is to develop opportunities and support for the recruitment, retention, re-entry, and advancement of women in biomedical careers. Since 1992, the ORWH has collaborated with scientific, medical, advocacy communities, other government entities, and the public to build programs related to careers for women in science. The ORWH is continuing to build this program through a variety of initiatives, which are described in the following.

The ORWH addresses the career development of girls and women in biomedical careers across their life span, from initial interest in science during grade school to postgraduate scientific training. In addition, the ORWH focuses its efforts on career development for both women and men engaged in careers in women's health or sex/gender research. In collaboration with NIH ICs and Offices, the ORWH has developed and implemented numerous educational outreach programs for girls in middle school and women in high school, college, graduate school, and postdoctoral programs. The ORWH has also implemented a special re-entry program for women and men who take time off from their careers to deal with family responsibilities. In addition, the ORWH developed the Achieving Excellence in Science (AXXS) program to engage scientific societies in advancing women in their careers.

The foundation for accomplishing these goals was laid in recommendations from public hearings and a career development workshop titled *Women in Biomedical Careers: Dynamics of Change; Strategies for the 21st Century*. Gender bias in the sciences impedes professional advancement for women long before they enter 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 or not 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 during hearings and the workshop are summarized as follows:

- Recruitment of women and girls into biomedical sciences;
- Lack of female role models and mentors;
- Career paths and rewards, such as salaries and promotions;
- Family responsibilities and dual roles;
- Need for re-entry into biomedical careers;
- Sex discrimination and sexual harassment;
- Gender sensitivity;
- Racial bias and special needs of minority women; and
- Research initiatives on women's health.

The ORWH has undertaken numerous activities to increase opportunities for women, including minority women. These activities address paths leading to biomedical careers as well as ways to promote interest in and sustain research participation of both women and men working in women's health. With expanding horizons in biotechnology and science, there is a need for greater participation of women in research that will open new frontiers in scientific technology as it relates to health and disease. Although exact figures are not available on women pursuing careers in biomedical research, the ORWH recognizes that there is a need to increase not only the

number of women who are biomedical and behavioral investigators but also the number of women who are in policymaking positions. Individuals in these positions can influence or determine the direction of research initiatives. Programs are needed to provide support for mentored research training and career development in areas related to women's health, for biomedical scientists who have interrupted their research careers to fulfill family obligations, for outreach to young girls and women who have an interest in pursuing careers in biomedical science, and for collaboration with professional societies that support career advancement of women scientists.

The ORWH provided the initial funding for the National Academies (NA) study that resulted in the report, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*. The authoring committee, which was chaired by Donna Shalala, Ph.D., President of the University of Miami and former Secretary of the DHHS, examined factors affecting training and career opportunities for women in science.

The Committee looked at how women enter scientific careers and advance through the ranks. In a competitive scientific era, it is critical to nurture the best and the brightest and the most innovative talent. The U.S. has made progress in increasing the number of women earning science and engineering degrees, but there is less evidence of progress when looking at academic positions held by women. The committee reviewed data available on gender issues across all fields of science and engineering, examining different employment venues for researchers with special attention to academe. This committee released its report in September 2006, providing findings and recommendations for recruiting, hiring, promoting, and retaining scientists and engineers. Research organizations, including the NIH, are now reviewing the recommendations.

Reentry into Biomedical and Behavioral Careers

In 1992, the 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 the NIH. The ORWH Re-Entry Supplement Program was reissued in FY 2004 and is currently supported by 23 NIH ICs. This program provides administrative supplements to existing NIH research grants to provide full- or part-time research support for individuals in programs geared to bring participants' research skills and knowledge up to date. It is anticipated that at the completion of the supplement, the scientists will be able to apply for a career development (K) award or for a research award. To date, the ORWH has supported more than 50 women and men through the re-entry program. Examples of re-entry supplements from FY 2005-2006 include the following:

Fred Hutchinson Cancer Research Center
The Role of Dab2 Tumor Suppressor
NIGMS Re-entry Candidate: Susan Veals-Onrust, Ph.D. (Year 2 in 2005)
PI: Jonathan Cooper, Ph.D.

Dr. Onrust received her Ph.D. at NYU in 1992 and did a postdoctoral fellowship at UCSF. She was absent from research for eight years. Under the re-entry supplement, Dr. Onrust is investigating the role of Dab2 as a tumor suppressor. This project fits her background in cell culture and biochemical skills.

Medical College of Georgia
Molecular Basis of Estrogen's Dual Effects on Coronary Arteries
NHLBI Re-entry Candidate: Mary Owen, Ph.D. (Year 1 in 2006)
PI: Richard E. White, Ph.D.

Dr. Mary Owen obtained her Ph.D. from Medical College of Georgia in 1979. After two years of postdoctoral training at UCLA, she became a research assistant professor at the University of Vermont Medical School. In 1984, Dr. Owen became an Assistant Professor at the University of Illinois at Rockford and in 1988 an associate professor at Philadelphia College of Pharmacy and Science. Dr. Owen took leave for seven years and recently returned to the Georgia campus of Philadelphia College. Before her leave, Dr. Owen had been an active researcher in the field of cardiovascular disease. Her research was supported by the NHLBI and the AHA. Her research under the re-entry program will look at the molecular effects of estrogen on coronary arteries.

Oregon Health and Science University
Steroid Responsive Mechanisms in the Ear
NIDCD Re-entry Candidate: Carol McArthur, M.D. (Year 1 in 2006)
PI: Dennis R. Trune, Ph.D.

Dr. Carol McArthur received her M.D. from the UCLA School of Medicine in 1984. She completed her residency at UC Davis, and she received a fellowship at the Harvard School of Medicine in pediatric otolaryngology. In 1996, she left academic medicine. In 2002, she reestablished her clinical practice on a half-time basis. At the same time, she began volunteering in Dr. Trune's laboratory in the otolaryngology department. This supplement will facilitate her re-entry into academic research by supporting a study on how the ear responds to steroids.

Thomas Jefferson University
Bone Growth in Dental, Cranial, and Skeletal Tissues
NIDCR Re-entry Candidate: Theresa Freeman, Ph.D. (2005 and 2006)
PI: Irving M. Shapiro, Ph.D.

Dr. Freeman received her Ph.D. from the University of Medicine and Dentistry of New Jersey and Rutgers University in 1996. After completing a brief postdoctoral fellowship at New Jersey Department of Human Services, she took a position as a research assistant professor at the University of Pennsylvania. After a seven year hiatus, she took a part-time consulting position. In 2004, Dr. Freeman was hired by Thomas Jefferson University as a research associate where she provided support to a large number of researchers. The re-entry supplement will enable her to devote time to her own research project on bone growth to build a career in biomedical research.

UCLA Orthopedic Hospital
Biochemistry of Normal and Abnormal Variants of Factors IX
NHLBI Re-entry Candidate: Madhu Bajaj, M.D. (2005 and 2006)
PI: S. Paul Bajaj, Ph.D.

Dr. Madhu Bajaj received her M.D. in 1976 from Armed Forces Medical College in Poona, India. She then completed residency and fellowship training at the UC San Diego Medical Center and St. Louis University Medical Center. In 1991, she was appointed assistant professor in the Division of Pulmonary, Critical Care and Occupational Medicine at St. Louis University School of Medicine. She received tenure in 2000 but needed to attend to family matters. After a move to Los Angeles, she was able to secure a clinical position as a visiting professor at the University of Southern California. However, she wished to reenter research. This re-entry supplement will support her study of the activation of factor IX by tissue factor VIIa in the extrinsic pathway of blood coagulation.

University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School
Treatment of Addiction to Nicotine in Schizophrenia: Modifying MET for Use with ASI Data
NIDA Re-entry Candidate: Adriana Cordal, M.D. (2005 and 2006)
PI: Douglas Ziedonis, M.D.

Dr. Adriana Cordal received her M.D. in 1985 from the Universidad de la Republica in Montevideo, Uruguay. She completed residencies and fellowships at St. Luke's Roosevelt Hospital Center before beginning as a full time academic faculty member at the University of Medicine and Dentistry of NJ in 1994. In 2003, she joined the Robert Wood Johnson Medical School faculty. Although having a clinical position, Dr. Cordal wanted to pursue an independent academic career in research. This supplement will support her research on nicotine addiction in schizophrenia.

Women's Reproductive Health Research Career Development Centers (K12)

The ORWH joined the NICHD in issuing an RFA to invite institutional career award applications for Women's Reproductive Health Research (WRHR) Career Development Centers. These centers support research career development for obstetrician-gynecologists (ob/gyn) 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 to research independence through a mentored research experience leading to an independent scientific career in women's reproductive

health. The emphasis is on research relevant to obstetrics and gynecology and/or its subspecialties, including maternal-fetal medicine, gynecologic oncology, reproductive endocrinology, and infertility. Related fields are also appropriate, including adolescent gynecology, urogynecology, and the reproductive health of women with disabilities. Academic departments and mentors with established research programs covering a broad range of basic and applied biomedical and biobehavioral science related to obstetrics and gynecology form the intellectual and technical base for mentoring junior faculty accepted into this program.

By June 2006, 33 new scholars had been appointed to the program; 17 were appointed in 2004 and 16 in 2005. The University of Cincinnati, College of Medicine WRHR Program hosted the May 2005 WRHR Scholars' Research Symposium and Directors' Meeting. The Wayne State University WRHR Program in Detroit hosted the June 2006 WRHR Scholars' Research Symposium and Directors' Meeting. A new national WRHR Web site is hosted by the University of Rochester WRHR Program. Information on the program is available online at http://www.wrhrscholars.org/contact.html.

The ORWH co-funded with the NICHD 10 new WRHR Centers in FY 2005 and 2006. Below is a brief description of each center.

Brigham and Women's Hospital/Harvard Medical School
Development of Scholars in Ob/Gyn for the 21st Century
PI: Robert L. Barbieri, M.D.

This continuing program builds on a long tradition of investigation and teaching in women's reproductive health. This program makes available biomedical resources in the extensive Harvard-affiliated system. The didactic component along with the clinical breadth and biomedical research capabilities of the system provide a rich foundation for career development. Individualized plans are created for each scholar and could include enrollment in a master's degree or Ph.D. program. Assignment to one of three career tracks based on the scholar's background optimizes the quality of the research experience. Mentoring from both research and academic career advisors creates a cohesive plan to solidify career development.

University of Alabama at Birmingham
Ob/Gyn Faculty Research Career Development Program
PI: John C. Hauth, M.D.

This center is based on a research infrastructure that can accommodate and sustain an independent program dedicated to training future generations of physician scientists. This program is located in a division within the Center for Research in Women's Health, thereby allowing scholars access to other research programs and senior mentors. The center's mission to maximize educational opportunities complements the institution's plan to provide a resource-rich environment for research training. This program offers a formal, structured pathway for entry-level and advanced scholars to acquire research skills needed to become independent investigators. A major strength of this program is the critical mass of senior academicians with enhanced interdisciplinary research skills, which benefits the development of scientists hoping to develop and sustain and independent research careers.

University of California San Diego
Reproductive Sciences Research Career Development Center
PI: Thomas R. Moore, M.D.

This center includes a flexible two-phase program to accommodate the needs of scholars with different scientific backgrounds and experience. This program provides opportunities for creative interdisciplinary approaches to diseases by bringing together basic scientists and ob/gyn clinical collaborators interested in women's reproductive health. Scholars who enter this program have access to clinical, translational, and basic science collaborators with expertise that ranges from the bench to bedside. This center has a Mentoring Committee to ensure scholars are exposed to an optimal research environment that will sharpen their research skills as they move toward independence. The program includes required didactic courses and opportunities for advanced degrees to round out the training experience.

University of Rochester
Rochester Women's Reproductive Health Research Program
PI: James R. Woods, M.D.

This center provides an outstanding pathway for ob/gyn physician scientists to commence a career in research. Scholars entering this program complete a basic core of didactic courses emphasizing clinical research design, data processing and analysis, writing, and ethics. This core curriculum provides important skills for both clinical investigation and practice. Given different levels of research experience and preferences of the scholars, the program offers two individualized tracks: laboratory science and clinical science. The research environment at this center offers a interdisciplinary research perspective and a population of mentors who are experienced educators and leaders in their respective fields. This program has a history of success in training physician scientists.

Baylor College of Medicine
Baylor WRHR Program
PI: Joe L. Simpson, M.D.

This center offers career development for ob/gyn clinicians pursuing molecular research related to women's reproductive health. The program is a partnership involving the Baylor College of Medicine and the M.D. Anderson Cancer Center, which offers additional clinical resources and laboratories. This program includes a formal didactic curriculum consisting of five required courses that complements the mentoring portion of the program. Each scholar has two mentors and an individualized training plan designed with their professional backgrounds in mind. The primary research mentor's role is to ensure the development of solid investigative expertise. The secondary mentor's role is to maintain the clinical perspective and monitor academic progress.

University of Colorado Denver/HSC Aurora
Colorado WRHR Career Development Center
PI: Ronald S. Gibbs, M.D.

This center has a flexible plan focused on basic, cellular, and molecular mechanisms as well as translational research for scholars seeking an independent research career in women's reproductive health. The program has established milestones for advancement in the program. Scholars are required to engage in an ongoing dialogue with mentors and to successfully complete the curriculum. Ultimately, scholars will write research proposals. The institution is developing several core laboratory facilities to assist scholars in the design and implementation of their research projects. The combined expertise of these cores will provide the infrastructure to meet the challenges of career development. This program has links to the new interdisciplinary graduate program in reproductive science. It is expected that this center will foster interactions among scientists and clinicians and offer scholars exposure to multiple disciplines in a rich intellectual environment.

University of North Carolina, Chapel Hill
RHR Career Development at UNC
PI: Robert C. Cefalo, M.D., Ph.D.

This center builds on the institution's climate of research growth and commitment to patient-oriented translational research. The PI has experience preparing physicians in obstetrics and gynecology for careers in clinical research and a track record of interdisciplinary reproductive health research. One objective of this program is to introduce new investigators to large-scale collaborative research teams. Mentor panels will be established so scholars can access scientific expertise and resources. The new Ob/Gyn Resource Core is available to provide comprehensive services to support the integration of laboratory methods into the scholars' research projects. This program includes a partnership with the Morehouse School of Medicine to identify eligible members of that ob/gyn faculty to participate in this program. Didactic components and a tailored training program increase the likelihood of future research independence for scholars participating in this program.

Northwestern University
Research Career Development in Obstetrics and Gynecology
PI: Sherman Elias, M.D.

This center provides a custom-designed research training and career development plan for each scholar. Scholars are exposed to research tools, graduate courses, and

grant-writing skills. The program is designed to accommodate scholars with a variety of research backgrounds. The scholars enter a basic science or clinical track based on their interests and previous research experience. The program provides access to a pool of experienced basic scientists as well as translational and clinical research mentors whose expertise spans a wide spectrum of reproductive science research. This group has an established track record for training independent investigators. The program's location in Chicago means that it is surrounded by six medical schools, which afford a large concentration of highly qualified potential scholars.

Colombia University Health Sciences
Columbia University Center for Career Development in Reproductive Sciences
PI: Mary D'Alton, M.D.

This ongoing center provides an opportunity for scholars to learn experimental concepts and techniques needed for an academic career in research. Mentors come from the Center for Reproductive Sciences within the Department of Obstetrics and Gynecology. The program has a history of combining basic investigation and training with reproductive sciences. The program recruits scholars who have an interest in basic sciences. The underlying theme is to maintain an essential clinical link to bridge basic research and its application and relevance to clinical principles related to women's health. Clinical advisors are available to help scholars achieve this linkage.

Women and Infants Hospital - Rhode Island/ Brown Medical School
Brown Medical School/WIHRI Dept. of Ob/Gyn WRHR Program
PI: Donald R. Coustan, M.D.

This center offers a flexible program to provide each scholar with a core curriculum essential for developing a career as an independent investigator in women's health. The program also provides a suitable mentor who can provide guidance and expertise as well as a research infrastructure appropriate for studies on women's health. The scholars can capitalize on a diverse group of senior scientific mentors and supporting investigators providing academic career advice. This program focuses on the translation of basic research into patient-oriented, clinical research to improve women's health.

NIH Director's Pioneer Award (NDPA)

The NDPA supports individuals who intend to pursue new research directions that are not already supported by other mechanisms, especially scientists of exceptional creativity who propose pioneering approaches to major challenges in biomedical and behavioral research. In FY 2006, the ORWH provided full funding ($500,000) to Rosalind A. Segal, M.D., Ph.D. of the Dana-Farber Cancer Institute. She is an associate professor of neurobiology at Harvard Medical School and a member of the Department of Pediatric Oncology at the Dana-Farber Cancer Institute. Dr. Segal received a Ph.D. in cell biology from Rockefeller University in 1985 and an M.D. from Cornell University Medical College in 1986. Her laboratory focuses on the biology of brain tumors, probing the complex molecular machinery of the developing brain. Dr. Segal's research aims to understand the mechanisms critical for normal development of the nervous system and how deregulated proliferation, migration, and survival of cells can cause brain tumors and other neurological diseases.

Achieving Excellence in Science (AXXS): Reports of Workshops

The ORWH collaborates with a number of professional and scientific societies to develop programs for advancing women in science. The ORWH, with the American Society for Cell Biology (ASCB) and the NIEHS, convened the *Achieving Excellence in Science (AXXS '99)* workshop to explore the roles of basic science societies in advancing research by building the careers of women in science. Career activities span the predoctoral stage to the senior scientist level. As a followup to the *AXXS '99* workshop, the ORWH supported *AXXS 2002*, a workshop to gather representatives of clinical societies to discuss ways for the societies to enhance the participation of women scientists in the clinical research workforce. In 2005 and 2006, members of the AXXS working group attended several annual meetings of professional and scientific societies, such as ASCB

and the Society for Developmental Biology where they presented AXXS materials. The workshop, held by the Committee on Women in Science and Engineering (CWSE) of the NAS, produced a report, *AXXS 2002: Role of Professional Societies in Advancing Women in Science*. Both reports from *AXXS '99* and *AXXS 2002* are available on the ORWH Web site at http://www4.od.nih.gov/axxs/.

Association for Women in Science (AWIS) Seminar Series

In FY 2005 and 2006, the ORWH provided support to the AWIS for its seminar series, which focused on career development issues for women. AWIS is dedicated to achieving equity and full participation for women in science, mathematics, engineering, and technology. The Bethesda Chapter of AWIS was formed in 1991 and has grown to more than 150 members. Its members are actively engaged in scientific research, education, administration, and policy activities and are employed in federal agencies, academia, business, and non-profit organizations. Seminars addressed a number of topic relevant to women in scientific careers, such as Making the Leap from Postdoc to Science Writer; Opportunities for Scientists in K-12 Science Education as a Career or as a Volunteer; Challenge of the Grand Challenges: A Career in Global Health Research; Successful Career and Family: How Do You Make It All Work; and Mentors: How to Find One, How to Be One.

American Society for Cell Biology (ASCB): Women in Cell Biology

The ORWH has worked with the ASCB to address career issues of women in science. The Women in Cell Biology (WICB) is a long-standing committee of the ASCB that provides year-round career support and advice. The WICB responds to reports of discriminatory practices, offers a speaker referral service to help program organizers identify women speakers, and produces monthly columns for the ASCB newsletter. In addition, the WICB has a traditional presence at the ASCB annual meeting, providing networking and workshop opportunities, which ORWH supported in FY 2005 and 2006.

Minority Faculty Student Partnership (MFSP) Program Workshops

The ORWH provides support each year for the MFSP Program Initiative. These workshops are co-sponsored by the Foundation for Advanced Education in the Sciences (FAES). This program includes a series of one-week lecture and "hands-on" laboratory training workshops in different areas of biotechnology. These lectures and workshops are topical and in great demand. The participants in the MFSP Program gain new insights into the current thrust of biotechnology. Information gained through this program can be taken back to their institutions and integrated into their programs. Approximately 25 students participate in these workshops each year. Additional information on this program is available online at: http://www.biotrac.com/MFSP/MFSPhome.html.

Women in Science and Health Care (WISH-net) Web Site

The ORWH, in collaboration with Public Responsibility in Medicine and Research (PRIM&R), established the WISH-net Web site at http://wish-net.od.nih.gov/. PRIM&R is a nonprofit organization based in Boston that is working to improve the diversity of both people and opinions in science and medicine. The WISH-net Web site is dedicated to girls and women interested in the field of science, providing resources to support and encourage those who may otherwise be discouraged from pursuing a career in the sciences. WISH-net seeks to inspire, mentor, and connect girls and women of all ages in science and health care. Throughout the site, WISH-net serves as a vehicle for stimulating and sustaining interest in scientific careers among school-age girls; encouraging women who are pursuing scientific study in college, doctoral programs, or postdoctoral fellowships or training; and supporting the commitment of women who are working in biomedical fields. WISH-net also promotes education, resources, professional and personal development, inspiration, and mentoring to girls and women of all ages and in all stages of their scientific journeys.

ORWH/Office of Science Education (OSE) Women Are Scientists Poster and Video Series

The ORWH and the NIH OSE have worked together to provide educational resources for precollege students and others who are interested in science and health. The series is designed to stimulate the interest of girls in science at a time when they are choosing academic courses that may affect their career options. 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 biomedical sciences and the educational requirements necessary to pursue them. The *Women Are Scientists* video series consists of five videos, Women Are Surgeons, Women Are Pathologists, Women Are Researchers, Women Scientists with Disabilities, and Women Are Dentists. The Women Scientists with Disabilities and the Women Are Dentists, the final ones in this series, are under development. Additional information about this series is available on the NIH Web site at http://science.education.nih.gov/women/scientists/index.html.

Intramural Program on Research on Women's Health

The goal of the NIH Intramural Program on Research on Women's Health (IPRWH) is to serve as a focus point for all intramural women's health research, including sex and gender comparisons, with the Intramural Research Programs (IRP) at the NIH. This program supports the ORWH mission in that it:

- Promotes, stimulates, and supports efforts to improve the health of women through biomedical and behavioral research within the ICs comprising the IRP;
- Enhances communication among and recruitment of intramural researchers working on women's health; and
- Develops and communicates training opportunities and recruits new clinical and basic research trainees into the IPRWH.

The IRPWH also has an active lecture series, which is described in the Outreach section that follows.

Research on Women's Health Fellowships

The ORWH and the IPRWH announced the selection of the recipients of the first NIH Women's Health Fellowships in Intramural Women's Health Research in 2006. These fellowships are funded through the Foundation of the NIH, with donations from Battelle and AstraZeneca, as the result of a new public-private partnership. The Shared Postdoctoral Fellowship, supported through a donation from Battelle, was awarded to Suzanne C. O'Neil, Ph.D., who is performing research jointly at the National Human Genome Research Institute (NHGRI) Social and Behavioral Research Branch and the NCI. The Clinical/Translational Fellowship, funded through a donation from AstraZenaca, was awarded to Shannon K. Laughlin, M.D., of the Epidemiology Branch of the NIEHS in Research Triangle Park, NC.

Graduate Partnerships Program Fibroid Fellowship

The Graduate Partnerships Program Fibroid Fellowship, which is supported by the ORWH and the NICHD, was established to provide for the support of continued studies of uterine fibroids. This fellowship was awarded to Chantal Mayers, who is participating in the Johns Hopkins University Graduate Partnerships Program. The Graduate Partnerships Program (GPP), established in 2000, links the NIH Intramural Research Program with Ph.D. programs at U.S. and international universities. Chantal Mayers is a graduate of Salisbury State University, where she discovered her interest in research. After graduation, she sought and was awarded one of the highly competitive postbaccalaureate Intramural Research Training Awards with Dr. James Segars in the NICHD. After three years of research with Dr. Segars and colleagues at the Uniformed Services University of the Health Sciences, Chantal joined the Johns Hopkins Graduate Partnerships Program to pursue her Ph.D. This scholarship enables her to continue her work with Dr. Segars.

Report from Second Task Force on the Status of Intramural Women Scientists

The ORWH supported the updated survey of the Second Task Force on the Status of Intramural Women Scientists to look at the composition of tenure-track and tenured senior investigators and to determine the need for mentoring and support networks. This study updated the areas covered in the first study conducted in the early 1990s, including communication, visibility, pay equity, tenure-track plan, and tenure. In addition, the second task force has identified impediments to the recruitment of women into tenure-track investigator positions and tenured senior investigator positions at NIH. The task force has also looked at impediments to the retention and tenure of female tenure-track investigators. In addition, it examined career tracks and appointment mechanisms chosen by men versus women and the underlying reasons for the choices. They are making recommendations for administrative and structural changes to correct identified problems.

Office of Intramural Training and Education Programs

The ORWH provides support for a series of annual training and education programs run by the Office of Intramural Training and Education (OITE). Each year, the OITE has provided several programs of importance to women seeking careers in science. These courses provide skills to scientists interested in research, including research on women's health and sex/gender factors. Examples of OITE workshops and the skills they seek to build follow.

SURVIVAL SKILLS WORKSHOPS FOR POSTDOCTORAL FELLOWS

- *Curriculum Vitae (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.

CAREER SERIES ON BIOMEDICAL RESEARCH CAREERS FOR POSTDOCTORAL FELLOWS

The ORWH sponsored three OITE workshops that described careers that would enable fellows to utilize their biomedical research training. This career series is available each year to intramural postdoctoral fellows.

- *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.

SCIENCE COMMUNICATION COURSES FOR POSTDOCTORAL FELLOWS

The ORWH provides essential support to the NIH Office of Education to provide programs to foster the professional development of postdoctoral fellows in both basic and clinical sciences. Written and oral presentation of research findings is key to a successful career in research. The following courses teach fellows how to communicate their findings to scientific and lay audiences.

- *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 to deliver scientific presentations using visual aids, including video feedback.

- *Advanced Speaking about Science*—This course has assisted fellows in building on the lessons of the introductory course, provided vocal and other technical instruction, discussed new methods of presentation, and offered a forum for indepth assistance on the individual needs of the participant.

- *Improved Language Skills*—This course was offered to first-year Visiting Fellows to enable them to improve the English skills needed for future professional development. The curriculum covered scientific vocabulary, diction, articulation, verbal pace, and general guidelines for speaking before a group.

Job Fair for Postdoctoral and Clinical Fellows

- The ORWH provides support to OITE for the NIH Annual Job Fair, at which more than 800 postdoctoral, research, and clinical fellows participate. The NIH Annual Job Fair is held in conjunction with the NIH Research Festival, which brings in companies that have biomedical research jobs available.

Career Enhancement Seminars for Postbaccalaureate Trainees

- The ORWH supports the OITE Career Enhancement Seminars that are designed to assist postbaccalaureate trainees as they prepare for careers in research. Topics of the seminars include speaking about science, presenting scientific data on posters, preparing for the MCAT and GRE tests, and taking the Myers-Briggs personality inventory.

Poster Day for Postbaccalaureate Trainees

- The ORWH provides support for the annual Poster Day for NIH postbaccalaureate trainees, which showcases the work of postbaccalaureate trainees who represent NIH ICs as they present their research accomplishments to the NIH scientific community.

Premed Advising Workshop for Postbaccalaureate Trainees

- The OITE Premed Advising Workshop for postbaccalaureate trainees who plan to apply for admission to medical school and/or M.D./Ph.D. programs is supported by the ORWH. The workshop provides information and helpful tips to follow during the admissions process.

ORWH-Foundation for Advanced Education in Science (FAES)-NIH High School Student Summer Program

The ORWH provides support for the ORWH-FAES-NIH Summer Program that is open to high school students from the D.C. metropolitan area. Students are selected on the basis of academic achievement, aptitude, and interest in a future career in science. Each student is assigned an advisor who provides guidance and assists in placing the student in an appropriate laboratory. Selected students work in a research laboratory at the NIH and have an opportunity to become involved in ongoing research projects. Each week during the summer, the students meet as a group for a lunch-time session where six to eight make presentations on their research. The presence of NIH senior scientific staff at the lunch-time sessions ensures a lively discussion of each presentation and helps the students put each research project into a broader biomedical context. All the students are expected to present posters at the NIH Summer Student Poster Presentation day. Thus, they learn not only how to carry out a research project, but also how to communicate their results to other scientists. The ORWH is providing support for this program.

NIH-Israel Program for Israeli Predoctoral Biomedical Researchers

The NIH-Israel Program for Israeli Predoctoral Biomedical Researchers program exposes predoctoral Israeli students at the Sackler Medical Faculty at Tel Aviv University (TAU) to the leading research programs in women's health at the NIH in cooperation with the OIR, the FIC, and the ORWH through the Graduate Program Partnerships Program. The program facilitates and enhances biomedical research in Israel, the Middle East, and the United States, establishes scientific collaborations between Israel and the NIH, and trains promising students for postdoctoral studies at the NIH. Each year, a joint TAU-NIH committee chooses approximately five of the best students to join the program. These students then perform research in the Israeli laboratory for 10 months each year and in the NIH laboratory for two months each year for a total of three years. The students that participated in the program have covered many aspects of cutting-edge research with a special emphasis on women's health.

Fellows Award for Research Education (FARE)

The ORWH provides support for FARE awards, which were established by the NIH Fellows Committee in 1994 as a mechanism for promoting and recognizing research excellence. All graduate students and postdoctoral fellows with less than five years research experience at the NIH are encouraged to submit abstracts to the FARE competition. The abstracts are evaluated anonymously by study sections composed of tenure-track and tenured NIH investigators, prior FARE winners, and other fellows. They are reviewed on the basis of scientific merit, originality, experimental design, and overall quality. The first authors of the top 25 percent of the abstracts in each study section are recognized as FARE winners. Each receives a $1,000 travel award to be used to present work at a scientific meeting during the fiscal year. The ORWH provided $50,000 per year to support 50 FARE awards in both FY 2005 and 2006.

Conferences and Workshops

ORWH-sponsored Research Planning and Development Conferences

During FY 2005 and 2006, the ORWH co-funded several scientific conferences and research planning workshops. The Office also sponsored several lectures during this period, including the 10th Annual John Diggs Lecture. Workshops and conferences supported by the ORWH are described below.

2005: Summary of Conferences and Workshops

NIH Family Hormonal Health Symposium: Pituitary Disorders
October 2004
NICHD

At the beginning of FY 2005, the ORWH, in conjunction with the NICHD, the Pituitary Network Association, and the National Naval Medical Center, convened a symposium on hormonal health. The purpose of the symposium was to increase awareness and scientific understanding of pituitary disorders to promote early diagnosis, disseminate knowledge on state-of-the-art treatments, and pique the interest of the research community about the pathophysiology of these complex disorders and their many ramifications. Abnormal hormone production caused by tumors of the pituitary gland has severe and debilitating effects on growth, reproductive and sexual function, and neuroimmune function as well as devastating effects on the patient's psychological state and psychosocial interactions. Findings from this meeting were incorporated into an ORWH publication titled *Family Hormonal Health*, which is currently being printed.

Advances in Uterine Leiomyoma Research: Second NIH International Congress
February 2005
NICHD

Uterine leiomyoma (fibroids) are the most common gynecologic neoplasm in women of reproductive age. As the number one

cause of hysterectomy, they have a profound negative impact on women's health. Uterine leiomyoma are hormonally dependent and, as such, are a potential target for endocrine-active compounds in the environment. The goal of this conference was to bring together researchers working in the fields of biomedicine, epidemiology, basic research, therapeutics, and translational medicine to foster an exchange of scientific information on uterine leiomyoma research. The conference, which was organized by the ORWH, brought together both the research and health care communities. Participants represented academia, medicine, industry, and government, including scientists from the AHRQ. Topics addressed at the conference covered clinical experience and therapeutic strategies, epidemiology, clinical trials, pathogenesis of smooth muscle tumors, and molecular and genetic characteristics. This conference provided a forum to update the scientific agenda on leiomyoma research.

Health Disparities in Infertility
March 2005
NICHD

This conference, which was organized by the NICHD and co-sponsored by the ORWH, addressed infertility. According to reports from the American Society for Reproductive Medicine, infertility is a major public health problem that affects up to 10 percent of Americans of reproductive age. However, very few studies have looked at the prevalence of infertility and receipt of related services by minority and low-income populations. This conference brought together clinicians from the NICHD's reproductive sciences portfolio and demographers from the Demographic and Behavioral Sciences Branch (DBSB) portfolio to discuss research issues, which are summarized in the conference report. The NICHD plans to convene another meeting of a broader representation of scientists working in infertility to assess the state of the science on this topic. The NICHD encourages interdisciplinary collaborations.

Fourth International Symposium on the Intraductal Approach to Breast Cancer
March 2005
NCI

This symposium was designed to encourage experts from a variety of relevant fields to bring their knowledge to bear on issues related to abnormalities found in intraductal cells associated with invasive breast cancer. The conference was sponsored by a number of organizations, including the Susan Love Foundation, the NCI, and the ORWH. The Susan Love Foundation is making an effort to reduce the impact of breast cancer by facilitating the dissemination of research findings and by supporting innovative research responsive to the breast cancer constituency at-large. The meeting included presentations from an active and growing network of investigators working on intraductal approaches to studying breast cancer. This symposium was part of a series of meetings to address this important topic.

Sixth International Symposium on Osteoporosis
April 2005
NIAMS

This meeting was sponsored by a number of organizations, including the NIAMS and the ORWH, and was convened in Washington, DC. The main goal of this conference was to gather individuals interested in the treatment, research findings, and public health issues related to osteoporosis. Presenters shared their latest research findings and discussed important issues related to treatments that may be developed in the future as well as new public health directions for osteoporosis.

Fourth International Conference on Cervical Cancer
May 2005
NCI

This conference on cervical cancer was organized by the NCI and sponsored by a number of organizations, including the ORWH. The goal was to provide an update on research in cervical cancer by bringing together leaders from the multiple disciplines involved with all aspects of cervical cancer causation, prevention, and screening. Objectives of the conference included:

- Description of the molecular epidemiology of cervical cancer;
- Discussion of optical techniques for screening and detection of cervical cancer;
- Description and discussion of chemoradiation for cervical cancer; and
- Enumeration and discussion of behavioral interventions for cervical cancer.

Addressing Health, Educational and Socioeconomic Disparities of Children in Immigrant Families
May 2005
NICHD

The purpose of this workshop, which was organized by the NICHD with support from the Office of Behavioral and Social Science Research (OBSSR) and the ORWH, was to encourage interdisciplinary research on children in immigrant families. Social scientists contributed to a number of areas related to this topic, including legal and policy constraints related to access to health care; important ethnic, cultural, linguistic, and economic differences across racial/ethnic groups; patterns of migration into and within the U.S.; and issues affecting children's access to health care and education. Developmental scientists addressed children's developmental trajectories, including individual variation in development and age-specific language skills. Research on children from immigrant families could be enhanced if the expertise of both social scientists and behavioral scientists are included in that research.

Gordon Research Conference on Calcium Signaling
July 2005
NIDCR

This biennial conference was convened in association with the complementary meeting of the Federation of the American Societies for Experimental Biology (FASEB) and received support from the NIH, including the ORWH. The conference location alternates between Europe and the U.S. This conference on calcium signaling provided a premier forum for scientists from diverse backgrounds to review exciting new developments in this area of research. The program included presentations from those scientists who were most active in the field but who had not presented at the most recent meeting of the Gordon Research Conferences or FASEB. The size of this conference was limited to 140 to emphasize and facilitate interactive discussions and lively scientific debate. There were eight break-out sessions with chairs selected to promote active discussion and one plenary session. Posters were a key feature of the conference. Most attendees presented posters during afternoon sessions; eight posters were selected for presentation as a talk. The focus of the conference was on the structure and function of proteins involved in calcium signaling and how they relate to our understanding of disease states. Sessions were devoted to the spatial organization of calcium signaling, the structure and function of intracellular and plasma membrane calcium channels, the roles of TRP proteins in normal and disease states, the roles of calcium in secretion and vascular function, and decoding calcium signals. These topics are of important to a range of diseases and conditions, including neurodegenerative and cardiovascular disease, aging, cancer, sensory disorders, and immunological diseases.

Sjögren's Syndrome
September 2005
NIDCR

The workshop on Sjögren's syndrome was organized by the Sjögren's Syndrome Foundation and was co-sponsored by several organizations, including the NIDCR, NCI, NIAID, the Office of Rare Diseases (ORD), and the ORWH, as well as several private sector organizations. This workshop focused on basic research on this syndrome. It was designed to foster the exchange of scientific data and catalyze discussions about potential triggers in the transition from autoimmunity to lymphoma. It also sought to generate fresh and novel concepts by bringing in speakers from a variety of related fields, including researchers in immunology, autoimmunity, and oncology. A clinical overview of the current treatment and knowledge about the close link between Sjögren's and lymphoma set the stage for subsequent discussions about basic scientific questions surrounding that link. To inspire young investigators to undertake basic research

related to the lymphoma-autoimmune transition, each speaker was invited to select a particularly talented investigator from his or her laboratory to attend and participate in workshop discussion and present posters during a special session.

2006: Summary of Conferences and Workshops

The Women's Health Initiative (WHI) Legacy to Future Generations of Women
February 2006
ORWH/NHLBI

This conference was sponsored in conjunction with the NHLBI and the ORWH and was convened in Bethesda, MD, on the NIH campus. The WHI is a landmark study in women's health and has important public health implications about the menopause and aging for women now as well as for future generations of women. This conference addressed many important findings from this study and included all center directors and PIs. Topic addressed included:

- Presentations on the results for the WHI dietary modification and calcium/vitamin D clinical trials;
- Findings from the two hormone trials, which had been released earlier;
- A synthesis of complex information generated from the WHI observational study and all four clinical trials;
- Discussions about the significance of the WHI findings for postmenopausal women's health;
- Recognition of the important contributions of the more than 161,000 women who participated in the WHI; and
- Overview of future WHI efforts, including opportunities for scientific collaboration, analysis of biospecimens, and the WHI Extension Study.

Developing New Standards for Autoantibody Measurement: Bringing Metrology to Serology
February 2006
NCI

Two of the largest health problems in the U.S. are autoimmune diseases and cancer, which, when combined, affect almost half of all Americans. Measuring circulating autoantibodies is an important part of clinical medicine, and there are many FDA-approved autoantibody tests that are currently available. The central technical feature shared by all autoantibody diagnostic assays is the capture of autoantibodies from serum using immobilized autoantigen. However, substantial variability in these tests has led to confusion about results and, therefore, questions concerning their utility in the diagnosis of disease. Currently, there are no autoantigen standard reference materials or standardized protocols. Moreover, there is little coordination among diagnostic developers, clinicians, and regulators regarding standards and best practices related to these tests. This workshop, which was convened by the National Institute on Standards and Technology (NIST), brought together leaders in autoantibody diagnostics, diagnostic testing, clinical laboratory medicine, and regulatory affairs to identify the fundamental and common metrology issues that underpin most antibody-based serodiagnostics. In addition, the workshop fostered partnerships and collaborations to develop the infrastructure and science needed to improve autoantibody-based diagnostics. This workshop was sponsored by the NIST, the NCI, the ORWH, and the American Autoimmune Disease Association.

Indigenous Suicide Prevention Research Programs in Canada and the United States
February 2006
NIMH

This conference was organized by the NIMH, the Indian Health Service, Health Canada, and the Canadian Institutes of Health and held in Albuquerque, NM. It was supported by a number of sponsors, including the NIH ORD, ORWH, OBSSR, NIDA, NIAAA, and the National Library of Medicine (NLM), as well as other U.S. agencies, such as the Substance Abuse and Mental Health Services Administration (SAMHSA). The conference brought

together representatives from research, service, community programs, and governments from a range of countries, tribes, and villages located in Canada, the U.S., and U.S. territories. Presentations illuminated the current state of knowledge concerning indigenous people and efforts related to suicide prevention. Although suicide rates in young, indigenous males are among the highest in the U.S. and Canada, the rates vary dramatically across communities. Conference attendees were asked to address what research efforts, from the communities' perspectives, are need to better address this tragic outcome that is very relevant to health disparities. Participants established a communication network to continue to share information about suicide and suicide prevention.

Progesterone Receptor Modulators and the Endometrium: Changes and Consequences
April 2006
NCI

This conference was organized by the NCI and convened in Bethesda, MD. The goal was to develop recommendations for regulatory interpretation of endometrial changes with chronic progesterone receptor modulator (PRM) treatment and to discuss what these recommendations might mean for future research. Questions were raised related to the validity of the concept of unopposed estrogen (E2) as an interpretation of endometrial response to treatment with PRMs. Conference topics included a review of the evidence regarding endometrial safety, classification of PRM endometrial effects, and methods to monitor endometrial safety in clinical trials and in clinical practice.

North American Integrative Medicine Conference
May 2006
NCCAM

The intent of this conference was to present the highest quality, peer-reviewed research in the field of complementary and alternative medicine (CAM). It was considered a major forum for CAM researchers in North America to gather and exchange ideas and data. The conference was sponsored by a number of organizations, including the NCCAM and the ORWH, and was attended by more than 600 researchers and CAM practitioners. The conference showcased original scientific research through keynote and plenary presentations, oral and poster presentations, and innovative interactive sessions. Presentations addressed basic science, clinical research, research methods, health services research, and education as it relates to CAM.

Regulation of Inflammatory Responses: Influence of Sex and Gender
September 2006
ORWH/NIAID

This workshop, which was co-sponsored by the ORWH and the NIAID, focused on the regulation of inflammatory responses and the influence of sex and sex-steroids on inflammatory responses. Managing these responses may influence disease risk. Participants at this workshop evaluated existing knowledge and concepts related to inflammation with the goal of developing innovative approaches to the prevention and treatment of acute and chronic diseases. They identified gaps in knowledge and research questions to be addressed in future research.

Meharry-Vanderbilt Alliance 4th National Health Disparities Conference: Why Our Babies Die
September 2006
NICHD

This three-day conference attracted approximately 200 investigators and physicians from across the country to discuss current research efforts on the disparities of infant mortality and morbidity in the U.S. This conference, Why Our Babies Die, was convened in Nashville, TN, and emphasized prevention efforts. Tennessee is ranked 48th in the nation in infant survival, and the state's preterm birth rate is 47th in the U.S. Members of the local research and clinical population wanted to address these critical problems at this conference. This conference was sponsored by the NICHD, the ORWH, and other NIH entities as well the March of Dimes, Adeza Biomedical, Matria Healthcare, and Governor's Office of the State of Tennessee. This support was critical to keep registration fees low for the many attendees from nonprofit agencies and health centers that serve medically underserved communities.

Fifth International Symposium on Hormonal Carcinogenesis
September 2006
NCI

This symposium focused on hormonal carcinogenesis in breast, prostate, ovarian, endometrial, colon, and lung cancers. INSERM, the French national health and medical research institute, organized the meeting and received support from the NCI and other organizations. It was held in Montpellier, France. The symposium addressed: (1) cellular origins of endocrine-related cancers, (2) mitotic kinases, centrosome amplification, and genomic instability, (3) new developments in steroid-receptor interactions, (4) risk assessment and relevant biomarkers for early disease, (5) novel strategies for prevention and treatment of endocrine-related cancers, (6) hormone dependency versus hormone independency, and (7) emerging fields in hormones and colorectal and lung cancers. Three state-of-the-art lectures were given during this conference. These lectures were titled Self-Renewal and Cancer Stem Cells, Ovarian Cancer: Linking Genomics to New Target Discovery and Molecular Markers: The Way Ahead, and Aurora, Polo, Nek, Cdk1 the Mitotic Bodyguards. Dr. Vivian W. Pinn, Director of ORWH, gave a special lecture on Women's Health Research: Perspectives from the National Institute of Health.

FMR1 Premutation and Premature Ovarian Failure: Worldwide Community Guideline Development
October 2006
NICHD

Increasingly, clinicians are responsible for engaging patients in discussions regarding available genetic tests, the results of which may have major implications for other family members. Premutations in the fragile X mental retardation 1 gene (FMR1) have been linked to altered ovarian function that may present as infertility, with low response to gonadotropin therapy, diminished ovarian reserve, or premature ovarian failure. This meeting, which was initiated by the NICHD, brought together recognized experts to present current perspectives on the management of women who may have altered ovarian function possibly related to an FMR1 premutation. Representatives from advocacy associations were invited to give presentations on community perspectives on this issue. Participants identified a need to establish standardized clinical definitions, terminology, and testing recommendations to facilitate research in this area. The meeting concluded with an open discussion of the proposed Worldwide Community Development Guidelines.

2006 NIDDK International Symposium: Frontiers in Painful Bladder Syndrome and Interstitial Cystitis
October 2006
NIDDK

This symposium, which was organized by the NIDDK, focused on the current state of research and clinical treatment for painful bladder syndrome and interstitial cystitis. The goals of the meeting included increasing scientific awareness of interstitial cystitis and its treatments, providing a forum to discuss the definition and etiology of interstitial cystitis and painful bladder syndrome, and exchanging information and ideas on current and future research to treat this disease and its symptoms. Plenary talks, selected short talks, and a poster session provided a forum for interactions among investigators working across these areas.

Other Activities

The Science of Sex and Gender in Human Health: An Online Course

In June 2006, the ORWH, in collaboration with the FDA's OWH, launched a new online course titled *The Science of Sex and Gender in Human Health*. The course offers participants scientific information on the major physiological differences between the sexes, the influence of these differences on illness and health outcomes, and their implications for policy, medical research, and health care. Designed for researchers, clinicians, academics, and students in health professional schools, the course builds on the IOM report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* (National Academy Press, Washington, D.C.: 2001.) This report received support from the ORWH, the DHHS OWH, the FDA, the

Society for Women's Health Research, and other federal and private agencies, and it was issued in 2001.

The course, which is free to the public, is self-administered. It is composed of six lessons that cover the definitions of sex and gender, the development and implementation of federal research regulations, cell physiology, developmental biology, pharmacodynamics and pharmacokinetics, and clinical applications of genomics. The course is available online at http://orwh.od.nih.gov/ and is approved for six AMA PRA Category I TM credits. Participants who complete the course receive a certificate from the NIH.

Since its launching in June 2006, 1,712 people have registered for this course during the first four months. Based on information on their Internet service providers, 273 registrants came from government agencies, 350 from educational institutions, 122 from other organizations, and the remainder from unspecified organizations. Thus far, 294 participants have completed the course. Thirty-eight of those completing the course hold medical degrees; 152 are non-M.D.s, and 104 did not seek credit. CME evaluations were submitted by 245 of the 294 individuals who completed the course. Their average score was 4.16 on a 5 point scale. This indicates that they met the course objectives. In addition, written comments and suggestions submitted by participants were quite favorable. It should be noted that to complete the course, participants were required to score 70 percent or higher on the quiz for each of the six lessons. The second course module is currently in development. It will apply the basic concepts presented in the initial course to specific conditions where sex differences play a significant role. The development of this module will be informed by information provided through the course evaluation.

PUBLIC INFORMATION AND OUTREACH

The ORWH works in partnership with the NIH ICs, other federal agencies, and various national, state, and community organizations utilizing a variety of outreach efforts to disseminate information on research on women's health. Working together, the ORWH and its partners ensure that timely and relevant information is distributed to advocacy groups, public and private institutions, and concerned individuals interested in women's health research. Outreach through ORWH advocates is a central method to disseminate the latest information and research findings on women's health. The 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 and clinicians to seek and use information from research on women's health and to see the ORWH as a central resource at NIH on women's health research.

Two important publications were produced in 2006, the ORWH's resource guide, *My Health, My Year, My Future and Women of Color Health Data Book Edition 2*. Subsequently, 20,000 copies of the resource guide were distributed within the first six months after publication. This document brings together current information from a variety of sources into one easy-to-use tool, addressing common health problems of women across their life span and practical steps they can take to improve their health.

The ORWH Director made approximately 40 presentations per year in 2005 and 2006 in a wide variety of venues, including annual meetings of the American Psychological Association, the American Heart Association, the National Medical Association, and the American Dental Education Association. The ORWH Director spoke at the Meharry Medical College where she received an honorary degree. ORWH staff attended more than 25 meetings in a year, making presentations at approximately half of these meetings. For example, in 2005, ORWH staff participated in a meeting on suicide, titled *Providing a Conceptual Framework in Suicide Prevention: Moving from Risk Factors to Programs*. Discussions focused on defining and disseminating information on the most effective methods of suicide prevention for different points in the life cycle. The 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. In FY 2006, the ORWH distributed more than 48,000 publication materials, some of which were distributed at more than 40 events throughout the U.S., including Washington, D.C., Maryland, Virginia, Texas, and Colorado.

Outreach to minority communities continues to be an area of focus for the ORWH. Utilizing a multipronged approach, the Office provides information, guidance, and direction to minority groups and organizations, assisting these communities in addressing health care needs for women. As an important component of outreach to minority communities, ORWH staff attends conferences and meetings, such as the Harvard Diversity Forum Conference, the National Hispanic Medical Association Conference, the Black Scientist Committee meeting, and the National Medical Association. The ORWH works in collaboration 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. Fifty percent of the events distributing ORWH materials, which are referenced above, were directed at minority communities, including the Heaven Project: Healing the Whole You in Atlanta, GA; Howard University; the Women's Health Institute in Washington, DC; Telemundo's Feria de la Familia and National Latinas Health Summit in Washington, DC; Bronner Brothers International Hair Show in Atlanta, GA; Delta Sigma Theta Health Fair in Washington, DC; and the National Medical Association in Dallas, TX. The third edition of the *Women of Color Health Data Book* was updated in 2006 and widely distributed. A Spanish translation of this most recent edition was completed. *Women of Color* contains information about many women's health issues, including those of particular interest to minority women, such as cancer, diabetes, obesity, cardiovascular disease, and infectious diseases. This document contains important data and information on factors affecting the health of minority women, including social and economic conditions, education, access to health services, and their associations with health outcomes. These and other ORWH and NIH documents inform the public of the NIH efforts to reach out to the minority community with techniques for recruiting and retaining minorities and women in clinical research.

The ORWH participates in several organizational and interagency committees, conference planning, and information dissemination activities on current research funded by the NIH. ORWH staff also provides services to other organizations, serving, for example, on the NIH OIR Combined Neuroscience IRB, which meets twice a month. In 2005 and 2006, the ORWH distributed materials throughout the country to public and private organizations and universities, such as the Mayo Clinic, Howard University, Health Centers of Northern New Mexico, Oregon Health and Science University, Wisconsin Women's Health Foundation, University of Virginia Medical School, Utah Navajo Health System, University of Mississippi Medical Center, the Washington Hospital Center, the Office of Women's Health at the Centers for Disease Control and Prevention, and the DHHS Office of Women's Health Centers for Excellence. For example, the ORWH contributed funding to the NIAAA to support the Governors' Spouses Initiative to Curb Underage Drinking. The ORWH also participated in the annual meeting of the Pituitary Network Association. Findings from this meeting were incorporated into an ORWH publication titled *Family Hormonal Health*, which is currently being printed.

The ORWH also provided materials for the following professional conferences: the National Medical Association, the National Latinas Health Summit, Howard University Women's Health Institute, Telemundo's Feria de la Familia, the National Hispanic Medical Association, Public Responsibility in Medicine and Research (PRIM&R), and Delta Sigma Theta Sorority.

In addition to presenting many speeches on women's health research to various groups, the ORWH meets with numerous representatives of the scientific and advocacy communities. In 2005 and 2006, the ORWH exhibited and provided women's health information at the National Women's Health Week, the National Woman's Heart Day, Sister to Sister Foundation, the Women's Health Initiative (WHI) Legacy to Future Generations of Women, the Office of Behavioral and Social Sciences

Research (OBSSR) 10th Anniversary, NIH IC of the Month, the North American Menopause Society, and the Montgomery County Women's Fair. For example, the Sister to Sister Foundation's campaign titled *Everyone Has a Heart* reached more than 21,000 attendees at their kick-off meetings in 12 cities across the U.S., screening more than 8,000 for risk factors for heart disease. Approximately half of those screened have two or more risk factors for cardiovascular disease.

ORWH Web Site

The ORWH focuses its outreach efforts to the scientific and public communities through its extensive Web site content, which is available at http://orwh.od.nih.gov/. Continuously updated with the latest conference information, upcoming seminars, and publication reports, the ORWH Web site currently averages 200 visits per day. The ORWH is redesigning the Web site for easier and more up-to-date access, flexibility, and multimedia use. The ability to locate the latest publications and women's health research news will be enhanced for the diverse stakeholders that use this site. A comprehensive restructuring of all sections will enable users to customize their searches and find online resources on diseases that affect the health of women, links of interest to women in biomedical careers, and mentoring programs utilizing state-of-the-art information technology.

The ORWH believes in a mosaic, interdisciplinary model of women's health. Visitors to the new site will be able to retrieve summary reports from all relevant NIH institutes on their research in women's health and key research findings from the ORWH-supported research programs, such as the BIRCWH and SCOR programs. The ORWH is committed to ensuring inclusion of women in clinical studies and provides the most recent reports in its inclusion of women in research section.

ORWH Women's Health Seminar Series

Since 1991, the ORWH has supported a women's health seminar series to provide the state of the science on issues of importance to the 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. Briefly, the topics of seminars and talks for FY 2005 and 2006 include the following. (A complete list for the entire seminar series is available on the ORWH Web site.)

Women and Sleep Disorders, March 2005

- Sleep Disturbances during Menstrual Cycle and Pregnancy
- Sleep Disturbances during Midlife and Older Age: What Next?
- The Lived Experience: The Patient Perspective
- Clinical Approaches to Women and Sleep Disorders

Women and Depression, June 2005

- Postpartum Depression in Pediatric Practices: Opportunities and Challenges
- The Menopausal Transition, Sex Steroids, and Depression
- Cultural Issues Related to Diagnosis and Treatment of Depression for Women
- Perspectives on Women and Depression from the Community

Women and Pain, November 2005

- Is Chronic Pain a Women's Health Issue?
- The Pains of Endometriosis
- Chronic Migraine and Women's Health
- Fibromyalgia: A Personal Look at Chronic Pain

Women and Sexually Transmitted Infections, March 2006

- Gender Differences and STIs
- Topical Microbicides
- Prevention of STIs in Adolescent Girls
- Community Perspectives on STIs among Adolescents and Young Women

CAREGIVING, JUNE 2006

- Family-Centered Service: What Is It, and Why Should I Care? Lessons from Families of Children with Disabilities
- Comparison of Emotional and Biological Parameters in Mexican American and White Male and Female Caregivers of Patients with Alzheimer's Disease
- Systematic Review of Advance Care Planning and Caregiver Burden and Satisfaction with Quality of Care at the End-of-Life
- The Task of Caregiving: Catastrophe or Celebration?

Women's Health Special Interest Group Seminars

As part of the Intramural Program on Research on Women's Health (IPRWH), the ORWH provides support for the Women's Health Special Interest Group (WHSIG) seminar series. The IPRWH sponsors bimonthly lectures by NIH and university researchers. In FY 2005 and 2006, WHSIG seminars addressed a range of topics, as noted in the following.

2005 Seminars

- Human Papillomavirus and Cervical Cancer
- Sex Hormones and Cognitive Aging
- Severe Combined Immunodeficiency
- Racial Disparities in Health Care
- Polycystic Ovary Syndrome
- Gender Differences in Lung Function

2006 Seminars

- X Chromosome Gene Dosage and Risk for Coronary Disease
- Endometriosis
- Etiology of Domestic Violence
- Fertility Preservation During Chemotherapy
- Post Traumatic Stress
- The X Chromosome and Sex-Specific Diseases
- Gonadal Steroids and Cognition and Emotion

Intramural Program on Research on Women's Health (IPRWH): Lecture Series

Since the IPRWH was established, it has had an active lecture series, which is conducted under the auspices of the WHSIG. Lectures given in FY 2005 and 2006 addressed a range of topics of interest to researchers working on women's health, including exercise, molecular epidemiology of HPV, the effect of hormones on cognitive aging, polycystic ovary syndrome, and endometriosis.

In addition, the NIH Women Scientist Advisors, with support from the ORWH, has developed a new seminar series to highlight outstanding research achievements of women scientists in the IRP at NIH. The seminar series is dedicated to the memory of Dr. Anita B. Roberts and honors her role as an exceptional mentor and scientist. The first lecture in this series was given in October 2006 by Dr. Elizabeth Nabel, Director of NHLBI, who spoke on genomic medicine and cardiovascular disease. The IRPWH has also obtained funding for several postdoctoral fellow and summer student positions.

Budget

SUMMARY OF NIH BUDGETARY EXPENDITURES ON WOMEN'S HEALTH, MEN'S HEALTH, AND RESEARCH APPLICABLE TO BOTH FY 2005 AND 2006

The amount of funding that the NIH invested in research during FY 2005 and 2006 is presented in this budget summary. Budget categories include funding for specific to women, men, or applicable to both. The budgetary figures presented in this report were provided and submitted by the budget officials at the individual NIH ICs, then compiled by the NIH Office of Budget and submitted to the ORWH 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:

(A) that are 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) for 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 conditions and applies to women of all ages and ethnic and racial groups.

The ORWH has collaborated with the U.S. DHHS Coordinating Committee on Women's Health, which includes the OWH in 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.

The approach to data collection for this report is similar to that employed for reports since 1993-1994. However, the methodology for calculating disease spending has 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 some of the earlier reports before FY 2003 and 2004, 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 two to one ratio 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, the ORWH requested the NIH ICs centers apply the criteria that follows, 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 labeled "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.

(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 combination of criteria. The 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 16 lists the overall NIH expenditures in FY 2005 and 2006 for specific diseases, disorders, and conditions. The health categories and subcategories in Table 16 were developed to accommodate all agencies in the 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 17 for FY 2005 and 2006, approximately 81.4 percent and 81.7 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 2005 to 2006, although the percent of total research dollars remained approximately the same for both. Table 18 provides summary data from the previous biennial report.

It is obvious from data complied that the greater part of NIH expenditures is on research that benefits both men and women alike. In both FY 2005 and 2006, an average of 81 percent was spent on research that was not gender specific but addressed health or scientific issues affecting both women and men.

For sex/gender-specific research during FY 2005, 12.8 percent and in FY 2006 12.6 percent of the NIH research budget was spent on women's health research that was sex/gender specific to women, while 5.9 percent in FY 2005 and 5.6 percent in FY 2006 was spent on men's health research that was sex/gender specific to men. 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. Actual amounts for each specific topical area are likely to underestimate the actual expenditures because no overlap in reporting is allowed by the prescribed method for data collection. In addition, the amount of NIH funds spent on women's health research should consider both the sex specific amount as well as the dollars listed under both. For example, in FY 2006, sex-specific research on women totaled $3,497,870, but studies on both men and women totaled $22,617,802. Thus, for NIH in FY 2006, a total of those figures would be a truer representation of expenditures.

TABLE 16

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

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Cancer								
Breast cancer (including mammography and other services)	667,923	0	812	668,735	694,547	0	833	695,380
Reproductive cancers:								
cervical	86,794	0	0	86,794	90,204	136	5,909	96,249
ovarian	103,803	0	0	103,803	100,233	0	0	100,233
vaginal, uterine, and other	51,166	0	162	51,328	39,886	0	0	39,886
Lung cancer	0	0	285,470	285,470	0	0	262,551	262,551
Colorectal cancer	0	981	271,456	272,437	0	1,126	262,951	264,077
Other neoplasms	112,945	62,276	3,432,915	3,608,136	105,053	93,107	3,411,066	3,609,226
Subtotal	**1,022,631**	**63,257**	**3,990,815**	**5,076,703**	**1,209,923**	**94,369**	**3,943,310**	**5,067,602**
Cardiovascular/Pulmonary								
Blood diseases	42,958	55,282	489,896	588,136	43,546	59,600	490,846	593,992
Heart disease	99,487	83,153	698,652	881,292	95,397	88,548	692,672	876,617
Stroke	58,599	59,619	162,435	280,653	64,680	65,103	147,059	276,842
Other cardiovascular diseases/disorders	121,050	94,300	662,728	878,078	121,134	100,587	638,296	860,017
Pulmonary diseases	52,636	53,322	474,216	580,174	51,698	54,585	478,238	584,521
Asthma	41,659	31,788	206,696	280,143	41,200	31,872	201,185	274,257
Other	8,708	8,042	172,026	188,776	8,795	8,629	199,878	217,194
Subtotal	425,097	385,506	2,866,649	3,677,252	426,450	408,924	2,848,174	3,683,440
Reproductive and Maternal/Child/Adolescent Health								
Contraception	28,866	7,099	524	36,489	27,150	7,145	2,317	36,612
Infertility	8,617	4,319	8,970	21,906	10,492	4,517	5,961	20,970
Female reproductive physiology	143,513	0	0	143,513	142,265	0	359	142,624
Hysterectomy	670	0	0	670	324	0	0	324
Endometriosis and leiomyomas	7,429	0	0	7,427	7,810	0	0	7,810
Pregnancy, pregnancy prevention, maternal health	186,992	242	12,158	199,392	180,685	251	6,722	187,658
Diseases related to DES exposure	5,816	0	0	5,816	5,389	0	0	5,389

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Female genital cutting	0	0	0	0	0	0	0	0
Other	8,206	47,177	612,772	669,155	7,502	47,313	605,717	660,532
Subtotal	390,109	59,837	634,424	1,084,370	381,617	59,226	621,076	1,061,919
Aging								
Menopause	36,951	189	1,434	38,574	38,732	147	1,113	39,992
Menopausal hormone and non-hormone therapy	17,512	2,716	108	20,336	13,245	3,069	0	16,314
Alzheimer's disease	34,421	10,651	547,545	592,617	30,751	11,717	543,887	586,355
Malnutrition in the Elderly	1,058	0	30	1,088	880	566	0	1,446
Osteoarthritis	29,155	0	22,760	51,915	27,132	106	22,267	49,505
Osteoporosis	147,324	1,637	2,085	151,046	138,137	4,337	2,433	144,907
Women's Health Initiative	38,686	0	0	38,686	12,124	0	0	12,124
Other	56,652	8,936	468,349	533,937	56,575	17,760	456,998	531,333
Subtotal	361,759	24,129	1,042,311	1,428,199	317,576	37,702	1,026,698	1,381,976
Metabolism/Endocrinology								
Diabetes	97,987	135,806	128,783	362,576	82,265	113,760	142,890	338,915
Obesity	174,090	92,409	70,391	336,890	150,304	80,278	147,504	378,086
Hepatobiliary disease	1,700	0	215,182	216,882	1,700	221	214,309	216,230
Thyroid diseases and conditions	13,920	3,480	5,436	22,836	13,969	3,492	6,009	23,470
Other	3,783	3,707	50,924	58,414	3,895	3,988	59,259	67,142
Subtotal	291,480	235,402	470,716	997,598	252,133	201,739	569,971	1,023,843
Substance Abuse								
Etiology (unspecified)	1,618	364	90,885	92,867	1,472	361	98,129	99,962
Epidemiology (unspecified)	1,131	348	30,418	31,897	473	334	25,777	26,584
Prevention (unspecified)	907	7	42,105	43,019	883	0	32,037	32,920
Treatment (unspecified)	2,551	720	25,014	28,285	1,799	694	21,367	23,860
Alcohol	2,858	669	99,115	102,642	3,182	1,574	101,760	106,516
Illegal drugs	173,489	410,304	422,285	1,006,078	174,369	407,749	413,427	995,545
Prescription drugs	0	0	0	0	0	0	7,191	7,191
Tobacco products	196	0	24,687	24,883	0	0	18,642	18,642
Other substances	0	0	2,335	2,335	0	0	3,294	3,294
Co-occurring substance abuse and mental disorders	1,046	0	7,028	8,074	689	0	5,240	5,929

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Subtotal	183,796	412,412	743,872	1,340,080	182,867	410,712	726,864	1,320,443
Behavioral Studies/Programs								
Violence (includes domestic abuse, abused women, and spousal abuse)	6,506	1,294	30,578	39,378	6,311	1,198	30,257	37,766
Tobacco use cessation	147	0	450	597	0	0	225	225
Physical activity and nutrition (promoting healthy behavior)	623	275	82,943	83,841	1,650	0	84,419	86,069
Other behavior change and risk modification	5,226	3,950	196,764	205,940	7,096	3,924	206,183	217,203
Caregiving	374	1	6,175	6,550	885	0	5,913	6,798
Other	5,901	0	324,580	330,481	4,487	410	294,300	299,197
Subtotal	18,777	5,520	641,490	665,787	20,429	5,532	621,297	647,258
Mental Health								
Etiology (unspecified)	0	0	6,207	6,027	10	0	6,910	6,920
Epidemiology (unspecified)	175	0	144	319	10	0	782	792
Prevention (unspecified)	0	0	131	131	10	0	923	933
Treatment (unspecified)	0	0	101	101	10	0	1,312	1,322
Depression and mood disorders	22,375	1,899	173,810	198,083	20,873	2,030	170,562	193,465
Suicide	654	665	14,584	15,903	711	196	14,237	15,144
Schizophrenia	9	9	142,124	142,142	486	9	137,964	138,459
Anxiety disorders	3,019	3,873	44,668	51,560	3,351	3,183	48,227	54,761
Eating disorders	7,945	170	4,808	12,923	8,657	74	4,867	13,598
Psychosocial stress	6,735	188	28,175	35,098	7,579	179	27,753	35,511
Posttraumatic stress disorder	5,185	1,350	16,746	23,281	5,607	1,182	18,593	25,382
Other mental disorders (excluding Alzheimer's)	15,141	4,566	627,620	647,326	13,444	5,965	613,468	632,877
Autism	0	306	24,030	24,336	2,821	5,000	43,833	51,654
Subtotal	61,237	12,720	1,059,117	1,133,074	63,569	17,818	1,089,431	1,170,818
Infectious Diseases								
AIDS/HIV	260,166	108,554	2,100,996	2,469,716	247,201	70,928	2,134,543	2,452,672
Tuberculosis	3,347	4,226	122,934	130,507	4,572	4,226	117,990	126,788
Sexually transmitted diseases (STD)	39,057	12,972	124,798	176,827	64,412	10,923	114,221	189,556

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Topical microbicides	56,697	1,266	3,310	61,273	73,466	2,010	7,023	82,499
Toxic shock syndrome	1,101	0	0	1,101	327	0	0	327
Tropical diseases	8,341	22,537	471,103	501,981	9,150	7,817	526,382	543,349
Other	2,479	4,012	951,464	957,955	2,235	2,088	759,254	763,577
Subtotal	371,188	153,567	3,774,605	4,299,360	401,363	97,992	3,659,413	4,158,768
Immune Disorders								
Arthritis	38,647	7,539	233,633	279,819	39,260	6,543	228,492	274,295
Lupus erythematosus	59,041	1,504	25,495	86,040	65,287	1,944	26,153	93,384
Multiple sclerosis	19,586	11,207	68,482	99,275	21,859	10,205	65,594	97,658
Myasthenia gravis	1,511	1,358	1,795	4,664	2,263	1,970	3,108	7,341
Scleroderma	7,724	0	1,113	8,837	6,432	0	3,007	9,439
Sjogren's syndrome	1,075	0	145	1,220	301	0	120	421
Takayasu disease	0	0	0	0	0	0	250	250
Other	0	0	910,944	910,944	293	0	33,970	34,263
Subtotal	127,584	21,608	1,241,607	1,390,799	135,695	20,662	360,694	517,051
Neurologic, Muscular, and Bone								
Trauma research	9,559	14,062	167,255	190,876	9,975	14,725	174,875	199,575
Muscular dystrophy	2,879	20,124	7,799	30,802	3,003	19,772	7,690	30,465
Chronic pain conditions	10,414	8,170	82,502	101,086	9,475	7,387	73,093	89,955
Temporomandibular disorders	465	104	1,490	2,059	246	0	1,627	1,873
Fibromyalgia and eosinophilic myalgia	7,974	204	646	8,824	7,909	197	189	8,295
Migraine	1,531	1,278	1,462	4,271	1,639	982	1,130	3,751
Sleep disorders	3,090	2,143	37,713	42,946	3,584	2,620	40,866	47,070
Paget's disease	0	0	2,659	2,659	0	0	3,582	3,582
Parkinson's disease	21,283	23,423	119,358	164,064	20,339	21,962	108,721	151,022
Seizure disorders	23,834	20,138	55,159	99,131	23,416	19,541	52,452	95,409
Other	39,347	42,262	683,839	765,448	45,502	48,472	732,896	826,870
Subtotal	120,376	131,908	1,159,882	1,412,166	125,088	135,658	1,197,121	1,457,867
Kidney and Urologic								
Urinary tract infection	9,974	203	4,181	14,358	7,358	203	5,345	12,906
ESRD and transplantation	4,773	5,551	104,398	114,722	5,648	5,551	95,188	106,387
Urinary incontinence (cystitis, pyelonephritis)	12,405	109	256	12,770	10,872	111	82	11,065
Other	26,643	6,119	220,597	253,359	24,294	5,885	249,217	279,396

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Subtotal	53,795	11,982	329,432	395,209	48,172	11,750	349,832	409,754
Ophthalmic, Otolaryngologic, and Oral Health								
Eye diseases and disorders	12,500	17,362	661,010	690,872	11,925	17,244	655,163	684,332
Ear diseases and disorders	17,040	0	353,746	370,786	20,636	0	339,565	360,201
Dental and oral health	0	0	11,868	11,868	0	0	10,643	10,643
Other	23,756	48,670	279,045	351,471	23,511	2,692	279,842	306,045
Subtotal	53,296	66,032	1,305,669	1,424,997	56,072	19,936	1,285,213	1,361,221
Health Effects of the Environment								
Environmental estrogens	10,728	429	21,070	32,227	9,875	1,093	21,420	32,388
Health effects of toxic exposure (excluding cancer)	4	4	49,448	49,456	17	18	42,901	42,936
Toxicological research and testing program	467	388	90,260	91,115	458	381	84,451	85,290
Chemical and biological warfare agents	0	0	13,633	13,633	0	0	11,529	11,529
Other	3	0	3,029	3,032	0	0	2,610	2,610
Subtotal	11,202	821	177,040	189,463	10,350	1,492	162,911	174,753
Cross-Cutting Categories and Special Initiatives								
Treatment, prevention, and services	5,390	6,256	285,358	297,004	3,080	2,629	303,949	309,658
Access to health care and financing	8	35	1,772	1,815	7	2	2,204	2,213
Education and training for health care providers	0	0	4,379	4,379	0	0	4,967	4,967
Health literacy and bilingual information	0	0	14,097	14,097	0	0	13,295	13,295
Cultural influences	56	0	2,722	2,778	0	0	2,472	2,472
Disability research and services	2,605	8,540	68,937	80,082	3,165	7,095	70,731	80,991
Homelessness	0	0	1,265	1,265	0	0	1,046	1,046
Chronic fatigue syndrome	1,507	568	1,416	3,491	1,435	524	2,323	4,282
Breast feeding	879	0	458	1,337	444	0	220	664
Organ donation	0	0	492	492	0	0	458	458
Genetic services and counseling	2,824	0	1,678	4,502	0	0	1,519	1,519

	FY 2005	Actual			FY 2006	Actual		
	Women	Men	Both	Total	Women	Men	Both	Total
Unintentional injury	0	0	20,542	20,542	0	0	20,447	20,447
Alternative and complementary therapies	35,697	25,786	93,913	155,396	36,153	25,629	85,799	147,581
Health statistics and data collection	619	567	11,158	12,344	933	582	10,769	12,284
Office of Women's Health	8,364	0	0	8,364	1,181	0	0	1,181
Other cross-cutting	54	0	2,652,665	2,652,719	150	34	2,690,702	2,690,886
Global health	262	0	0	262	18	0	944,896	944,914
Subtotal	58,265	41,752	3,160,852	3,260,869	46,566	36,495	4,155,797	4,238,858
TOTAL: Women's and Men's Health	3,550,592	1,626,453	22,598,881	27,775,926	3,497,870	1,560,007	22,617,802	27,675,571

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

TABLE 17

NIH Research Budget Summary by Sex/Gender, FY 2005 and 2006

(Dollars in thousands)

FY	Women		Men		Both		Total	
	Dollars	Percent	Dollars	Percent	Dollars	Percent	Dollars	Percent
2005	3,550,592	12.8	1,626,453	5.9	22,598,881	81.4	27,775,926	100.0
2006	3,497,870	12.6	1,560,007	5.6	22,617,802	81.7	27,675,571	100.0

TABLE 18

NIH Research Budget Summary by Sex/Gender, FY 2003 and 2004

(Dollars in thousands)

FY	Women		Men		Both		Total	
	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	100.0
2004	3,478,203	12.7	1,572,719	5.8	22,234,583	81.5	27,285,505	100.0

Executive Summary

OVERVIEW

The scope and expansion of women's health research across the NIH has been remarkable over the past two years. This report is evidence of the progress that has been achieved. In this Overview, we describe the missions of the NIH Institutes and Centers (ICs), with a special focus on how they address women's health issues. The Highlights of Institute and Center Activities section that follows provides a synopsis of their research agenda and accomplishments in women's health that have been achieved in FY 2005 and 2006. Readers are encouraged to review the detailed reports of the individual NIH ICs that follow. These present important advances in understanding diseases and conditions that disproportionately affect women.

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 other NIH Institutes. In addition, the FIC and the ORWH have teamed up to explore issues facing women in science in developing countries and to consider gender and global health issues. These initiatives have informed the programmatic directions of the FIC and other NIH ICs.

Cancer continues to take a devastating toll on American women. However, important progress is being achieved in the fight against cancer overall as well as specific cancers differentially affecting women. These include cancer of the breast, cervix, ovaries, endometrium, colon and rectum, and lung as well as malignancies associated with acquired immunodeficiency syndrome (AIDS). In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these grim statistics, the U.S. is making important progress against cancer. Incidence rates for cancer of all sites, sexes, and populations combined were stable from 1992 through 2003 after increases that started in 1975. Incidence rates for cancer overall for women were stable from 1975 through 1979 but then increased from 1979 through 2003. However, there was a 6 percent relative decline in breast cancer incidence among women between 2002 and 2003, including a 14 percent decrease in 50- to 60-year-olds who had been diagnosed with estrogen receptor (ER) positive breast cancer. The decrease in this age group may be due to the recent decline in use of hormone therapy (HT) by postmenopausal women. Mortality rates for all cancers have declined, but the annual decline in men is twice as large as that for women. While mortality has decreased for 10 of the top 15 cancers in women, lung cancer deaths in women continue to increase, although at a slower rate in more recent years. Survival rates for cancer patients show improvement overall, although the amount of improvement is slightly less for women than men. The National Cancer Institute (NCI) supports an extensive research program through their intramural and extramural programs, with a number of programs and activities focusing on women's cancers, including the NCI Office of Women's Health, located within the NCI Office of Science Planning and Assessment; the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention; the Breast Cancer Surveillance Consortium (BCSC) and the International Breast Screening Network in the Division of Cancer Control and Population Sciences; the Gynecologic Oncology Group (GOG) and the Clinical Trials Cooperative Group in the Division of Cancer Treatment and Diagnosis; the intramural Breast and Gynecologic Malignancies Faculty and the trans-NCI Human Papillomavirus (HPV) Working Group. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, we hope to accelerate the pace of discovery and facili-

tate the translation of research knowledge into clinical applications.

The mission of the National Center for Complementary and Alternative Medicine (NCCAM) is to explore complementary and alternative healing practices in the context of rigorous science, train CAM researchers, and disseminate authoritative information to the public and professionals. Complementary and alternative medicine (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 interventions proven to be safe and effective become accepted as mainstream health care practices. The NCCAM groups CAM practices within the following areas: (1) whole medical systems (i.e., traditional Chinese medicine, naturopathic medicine, Ayurveda); (2) mind-body medicine (i.e., meditation, yoga); (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). The NCCAM conducts and supports basic and applied (clinical) research and research training within these areas. 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 CVD. CAM therapies for women treat a variety of conditions, such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and reproductive issues. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions.

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level to move to animal-based studies and on to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. The NCRR develops and supports a wide range of biomedical resources. 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 to address emerging clinical and basic research needs, including those addressing women's health issues.

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 multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. 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 supports the Research Infrastructure in Minority Institutions Program (RIMI) and the Minority Health and Health Disparities International Research Training Program (MHIRT). These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities for the benefit all affected populations, including women of diverse populations.

The mission of the National Eye Institute (NEI) is 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 (i.e., glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer on average than men, more women than men are affected by these age-related eye diseases in the U.S. 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 and in most cases 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 from age or trauma; 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.

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases. The NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a collaborative research infrastructure in partnership with private and public organizations. The Institute also collaborates with patients, families, health care professionals, scientists, professional societies, patient-advocacy groups, community organizations, and the media to maximize the use of research results and resources to address the public health needs of the nation. The NHLBI places high priority on improving the cardiovascular health of women through its research programs, which have generated new knowledge about the influences of lifestyle, menopause, chest pain, hypertension, diabetes, and drug treatment (including hormone therapy) in women and also have led to improved diagnostic tests and treatment guidelines for women. The NHLBI has had responsibility for the NIH Women's Heath Initiative since 1998 and provides support for the Women's Ischemia Syndrome Evaluation as well as other important studies.

The National Human Genome Research Institute (NHGRI) led the NIH's contribution to the International Human Genome Project (HGP). The finished sequence of the human genome was completed in April 2003, and has already begun to change the way we address research on women's health. In October 2005, a different international consortium of scientists from six countries, led by the NHGRI, announced the production of a different map of the human genome, one that may prove even more powerful because of its medical applications. The result is the "HapMap." Like the earlier sequence, all of the data from the HapMap has been placed in the public domain. The HPG spelled out the letters of the DNA code that all human beings share. The HapMap provides detailed information about the variation in the genome. The HapMap investigates those spelling differences in the human instruction book that predispose some people to different types of cancer as well as other diseases. In December 2006, the NHGRI awarded a contract to continue the HapMap Project to make it an even more powerful tool to reveal the way in which genetic variation is organized into chromosomal neighborhoods. As this information unfolds, the NHGRI will continue to investigate diseases specific to women. In 1994, NHGRI investigators were among the first to report that women carrying the gene mutations called Breast Cancer 1 (BRCA1) or Breast Cancer 2 (BRCA2) have a higher risk of developing both breast and ovarian cancer than women without such mutations. The NHGRI continues to investigate the role of these genes in breast and ovarian cancer, and this research has led to better screening and treatment of those with a family history of breast cancer. In hopes of expanding the usefulness of this research, the NHGRI also supports research that explores the effect of educating women of different ages and ethnic group about benefits of genetic screening in evaluating their risk of inherited diseases.

The National Institute of Allergy and Infectious Diseases (NIAID) funds basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses that affect the health of women and girls. The NIAID involves women in many of its clinical studies on the treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). The NIAID also collaborates with other organizations on research initiatives aimed at improving women's health.

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 that disproportionately affect women including osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint and muscle disorders (TMJD), fibromyalgia, scleroderma, and systemic lupus erythematosus (lupus). Scleroderma and lupus are diseases in which health disparities have been clearly identified. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

The National Institute of Biomedical Imaging and Bioengineering (NIBIB), which was established by law in December 2000, is the newest research institute within the NIH. This Institute serves as the hub within the NIH for the 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 for 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 FY 2005 and 2006, the NIBIB funded grants 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, such as osteoporosis. 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 the past two years, the NIBIB supported research on women's health in the following disease areas: aging, autoimmune disease, breast cancer, cervical cancer, reproduction, diabetes-related research, obesity, epilepsy, HIV/AIDS, heart disease, osteoporosis, and TMJD.

The National Institute of Child Health and Human Development (NICHD) sponsors research that spans human growth and development, starting from before conception and continuing through infancy, childhood, and adolescence. This research covers all critical stages of development that provide the foundation for adult health. The Institute's research aims to overcome many of the complex challenges that face women in addition to those faced by their children and families. The NICHD's portfolio includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are critical to improving the quality of life for women.

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 and infectious diseases affecting the mouth and face. NIDCR-supported research spans areas as diverse as understanding the oral infections that lead to dental decay, periodontal diseases, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone diseases; salivary gland dysfunction and disease; craniofacial birth defects and developmental disorders; and connective tissue diseases and disorders. The NIDCR has a long tradition of support and leadership in the field of pain research, including conditions where gender-based differences have been reported, such temporomandibular joint and muscle disorders (TMJD). The NIDCR's commitment to the fundamental study of the body's hard tissues, such as 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 molecu-

lar processes to repair and regenerate tissues and organs. Among the NIDCR's efforts in this area are studies that are characterizing the TMJ disk at tissue and cellular levels, thus providing vital information that will one day allow for biological approaches to reconstruct or regenerate the temporomandibular joint. Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the Institute has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. The research advances that affect women in particular are to be found within many of the Institute's broad research categories.

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 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; painful bladder syndrome/interstitial cystitis (PBS/IC); urinary tract infections (UTIs); urinary NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease (CVD). The NIDDK supports research that directly addresses important women's health issues, both through basic research directed to understanding underlying disease processes and through clinical research that translates this understanding into therapies and preventive interventions.

Because environmental agents are likely to play a role in a numbers of diseases that differentially affect females, the National Institute of Environmental Health Sciences (NIEHS) supports research on diseases such as breast cancer, osteoporosis, ovarian dysfunction, uterine fibroids, and autoimmune diseases. The Institute's approach is to define the underlying susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds 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. The Institute has several groups that focus on women's health, including the Laboratory of Reproductive and Developmental Toxicology, the Hormones and Cancer Group, the Chromatin and Gene Expression Group, and the Comparative Pathology Group. These research groups and others are conducting basic research on issues such as toxicology and reproductive and developmental health, hormone regulation of tumor development and growth in target organs, including the uterus and mammary gland, genetic regulation of cancer susceptibility, as well as epidemiologic research on women's health issues, such as fertility, early pregnancy, and uterine fibroids. By understanding the basic mechanisms of disease, new therapeutic interventions can be developed to prevent and treat these diseases.

The mission of the National Institute of General Medical Sciences (NIGMS) is to support research and research training for the basic biomedical sciences. For example, 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 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 National Institute of Mental Health (NIMH) supports research on a range of mental disorders, including those that affect

women exclusively, such as perinatal depression, or are more prevalent in women, such as eating disorders. Through programs, such as the Women's Mental Health Team, the NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and the prevention of mental disorders in women. Data on the epidemiology of mental disorders and associated disability highlight 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 and eating disorders than boys, while boys are more likely to suffer from autism and attention deficit disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. The course and severity of mental disorders also differ 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. Within the female populations, some women are at increased risk of depression during certain times of reproductive change, such as the perinatal period. Through its research programs and related programmatic activities, the NIMH seeks to improve scientific understanding of the effects of sex and gender differences in mental health and mental illness.

The National Institute of Neurological Disorders and Stroke (NINDS) mission is to reduce the burden of neurological disease, a burden borne by every age group, every segment of society, and 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. Examples of such diseases include multiple sclerosis (MS), pain, stroke, epilepsy, and Rett syndrome. MS is a chronic autoimmune disease of the central nervous system that causes inflammation and the loss of myelin, a protective covering around nerve fibers. MS is one of the most common neurological disorders leading to disability in young adults. Hormonal factors may influence some forms of MS, making them more common in women. 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 U.S. and a major cause of disability in both women and men. In general, women have a lower risk of stroke than men, but because of their longer life expectancy, they account for 60 percent of stroke fatalities. Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. Although anti-epileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for others, 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. Rett syndrome is a childhood neurological impairment seen almost exclusively in females, causing severe cognitive impairment, autistic behavior, stereotypic movements, and frequently seizures. The NINDS supports basic, translational, and clinical research on these and other neurological disorders.

The mission of the National Institute of Nursing Research (NINR) is to support clinical and basic research that establishes a scientific basis for the care of individuals across the life span. NINR-supported research encompasses the health of individuals, their families, and their caregivers. It also focuses on the special needs of at-risk and underserved populations, with an emphasis on health disparities. The Institute's research focus transcends many disciplines to promote health and improve patient and caregiver quality of life across a broad range of diseases and conditions. The NINR unites the disciplines of biological and behavioral sciences to elucidate the complex interactions between the physiological factors of health and disease and the behavior, decisions, and perceptions of the individual. In 2006, the NINR released its new five-year strategic plan, titled *Changing Practice, Changing*

Lives. Developed in close consultation with representatives of the extramural community, this new plan details the NINR's scientific priorities. The Institute will focus its research on health promotion and disease prevention; improving quality of life through self-management, symptom management, and caregiving; eliminating health disparities; and leading critical research on the end of life. The plan also highlights four cross-cutting strategies for advancing nursing science, including advancing the integration of biological and behavioral sciences, promoting the design and use of new patient care technologies, improving nursing science methods, and developing the next generation of investigators. The NINR's mission and research goals are inherently suited to addressing the current challenges in women's health research.

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies of Alzheimer's disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. NIA-supported investigators continue to explore the reasons behind gender differences in disability, morbidity, and mortality at older ages. In addition, the NIA supports an extensive program of research pertaining to health disparities among special populations. The NIA has several ongoing research initiatives dealing specifically with women's health, including the Study of Women's Health Across the Nation (SWAN), the Women's Health Initiative Study of Cognitive Aging (WHISCA), and Women's Health and Aging Study (WHAS). These studies and others are providing valuable information about the menopausal transition in women of diverse racial and ethnic backgrounds; the effects of hormone therapy on memory and cognitive functions; disability among older women; and other health issues of importance to older women, who are more likely than men to live alone and in poverty and to be institutionalized at an earlier age.

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. It is estimated that there are 18 million alcohol-abusing or alcohol-dependent individuals in the U.S., of which more than four 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's health. Research related to women's health is found in each programmatic division of the institute. Because of the multidimensional and multidisciplinary nature of alcohol use disorders and their prevalence worldwide, collaborative research endeavors on a national and international scale are required for progress toward the goals of reducing alcohol abuse disorders and alcoholism among women. Significant scientific advances in understanding the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women have occurred in the past two fiscal years.

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 Institute also conducts and supports research and research training that is related to disease prevention and health promotion. The research portfolio addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute also 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.

The National Institute on Drug Abuse (NIDA) addresses critical questions concerning drug abuse and addiction by monitoring emerging trends, identifying and studying underlying physiological and social factors,

and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. An important focus in NIDA's portfolio is research to investigate issues specific to women and to sex/gender differences in drug abuse and addiction. There is a complex relationship between drug use and biological vulnerability that may vary by sex or gender. Growing evidence suggests that drug abuse may begin and progress differently for men and women. These patterns of progression are characterized by different risk and protective factors and motivations and carry different consequences. In recognition of the important role that sex/gender plays in drug abuse, sex/gender research findings are being taken into account in the design, testing, and implementation of interventions to prevent and treat drug abuse and to provide services for both males and females. NIDA has established a Women and Gender Research Group to promote research on issues specific to women and substance abuse. This group has representation from all of NIDA's divisions and offices, covering topics from genetics and basic biology to risk factors, prevention, consequences, and treatment of substance abuse. The major goal of this effort is to infuse the study of sex/gender differences and female-specific issues in all areas of drug abuse research and to disseminate research findings.

In addition to the involvement of the NIH ICs mentioned before, several of the Offices within the Office of the Director of NIH participate in activities related to women's health and sex/gender issues. The Office of Dietary Supplements (ODS) supports research to expand the evaluation of the role of dietary supplements in disease prevention and risk reduction associated with diseases of interest to women, including breast cancer. In addition, ODS supports research to further scientific understanding of the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle. The Office of Behavioral and Social Sciences Research (OBSSR) opened on July 1, 1995. Congress established OBSSR in recognition of the key role that behavioral and social factors play in illness and health. The OBSSR mission is to stimulate behavioral and social sciences research throughout the NIH and to integrate these areas of research more fully into other NIH health research enterprises, thereby improving the understanding, treatment, and prevention of diseases. Many of these diseases are related to women's health, such as type two diabetes, coronary heart disease, obesity, addictive behaviors, and disorders of mood and affect. The Office of Rare Diseases (ORD) seeks to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have one of the approximately 7,000 rare diseases recognized today. Several of these rare diseases differentially affect women, including lymphangioleiomyomatosis, Rett syndrome, congenital adrenal hyperplasia, and preeclampsia. The ORD collaborates with the NIH ICs and Offices to stimulate research on rare diseases, to foster collaborations with other national and international entities, and to support a range of outreach activities related to rare diseases. The Office of AIDS Research (OAR) was established in 1988. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. This diverse basic, clinical, and behavioral research portfolio demands an unprecedented level of scientific coordination and management of research funds. The OAR coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, the OAR ensures that research dollars are invested in the highest priority areas of scientific opportunity. As such, the OAR represents the roadmap for NIH AIDS research, allowing NIH to pursue a united research front against the pandemic. The trans-NIH strategic plan for AIDS research establishes an agenda in the following areas of emphasis: vaccines; therapeutics; etiology and pathogenesis; natural history and epidemiology; behavioral and social science; training, infrastructure, and capacity building; and information dissemination. Research relevant to the needs of women is addressed in all of these areas.

Highlights of Institute, Center, and Office Activities

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. In addition, the FIC and the ORWH have teamed up to explore issues facing women in science in developing countries and to consider gender and global health issues. These initiatives have informed the programmatic directions of the FIC and other NIH ICs.

NATIONAL CANCER INSTITUTE

This biennial report describes many of the activities and accomplishments of the National Cancer Institute (NCI) research programs in FY 2005 and 2006 addressing cancers that are specific to women, primarily affecting women, or with high incidence or mortality rates among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as acquired immunodeficiency syndrome (AIDS) and AIDS associated malignancies.

Cancer continues to take a devastating toll on American women. In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in cancer affecting women. Incidence rates for cancer of all sites, sexes, and populations combined have been stable from 1992 through 2003 after increases that started in 1975. The pattern of aggregate incidence was similar for men. Incidence rates for cancer overall for women were stable from 1975 through 1979 and then increased from 1979 through 2003. However, breast cancer incidence rates for women had a statistically non-significant decrease from 2001 through 2003. Overall, there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003, including a 14 percent decrease in 50- to 60-year-old women who had been diagnosed with ER positive breast cancer. The decrease in this group may be due to the recent decline in use of hormone therapy (HT) by postmenopausal women. The overall cancer death rates for all sites, sexes, and race/ethnic populations decreased from 1994 through 2003, with the annual rate of decline in men being twice as large as the annual decline for women. Mortality has decreased for all cancers combined in the general population and for 10 of the top 15 cancers in women. Lung cancer death rates among women continue to increase, although at a slower annual rate in more recent years. Survival rates for cancer patients diagnosed in the years 1975 to 1979, compared with those diagnosed from 1996 to 2002, show improvement overall, although the amount of improvement is slightly less 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. The NCI's Office of Women's Health, located within the NCI 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 both intramurally at the NCI and extramurally through research grants, a number of specific programs and activities focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention; the Breast Cancer Surveillance Consortium (BCSC) and the International Breast Screening Network in the Division of Cancer Control and

Population Sciences, the Gynecologic Oncology Group (GOG) and the Clinical Trials Cooperative Group in the Division of Cancer Treatment and Diagnosis, and the intramural Breast and Gynecologic Malignancies Faculty and the trans-NCI Human Papillomavirus (HPV) Working Group.

In addition to research with a primary focus on women's health, the NCI supports broad-based research programs that apply to all types of cancer in women, men, and children. 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 reduce the burden of cancer in all populations. The NCI strategic plan (http://strategicplan.nci.nih.gov/), which was released in 2006, details eight strategic objectives in two broad areas: (1) To Preempt Cancer at Every Opportunity and (2) To Ensure the Best Outcomes for All. The NCI supports research programs to expedite progress toward the following objectives.

Research in the first area, To Preempt Cancer at Every Opportunity, focuses on four strategic objectives. To address the first objective, Understanding the Causes and Mechanisms of Cancer, research is being conducted to discover the causes and mechanisms of cancer. This is essential to develop and apply treatments or interventions to keep cancers from starting or progressing. The NCI research portfolio supports basic, clinical, and population research to better understand how genetic, epigenetic, environmental, behavioral, and sociocultural factors relate to cancer. The second objective, Accelerating Progress in Cancer Prevention, is addressed through the NCI's portfolio supporting research to identify medical and behavioral approaches to cancer prevention that can be applied in public health settings. Prevention research focuses on risk assessment, systems biology, behavior modifications, environmental and policy influences, medical and nutritional approaches, and training and education for research and health professionals. Ongoing research related to the third objective, Improving Early Detection and Diagnosis, supports the development and dissemination of interventions to detect and diagnose early-stage malignancy with the goal of improving the odds for successful treatment and reduction in mortality. And research related to the fourth objective, Developing Effective and Efficient Treatments, focuses on discovering, developing, and evaluating more efficient and effective treatment strategies with little or no harm to healthy tissue.

Research related to the second area, To Ensure the Best Outcomes for All, encompasses four additional strategic objectives. To address this area's first objective, Understanding the Factors that Influence Cancer Outcomes, the NCI is intensifying its efforts to define, foster, and support studies to improve the understanding of factors affecting the outcomes of cancer and the impact of cancer care. Research focuses on understanding and measuring environmental, behavioral, sociocultural, and economic influences that affect the quality of cancer care, survivorship, and health disparities. The second objective, Improving the Quality of Cancer Care, high-quality cancer care requires delivering the full range of evidence-based interventions that are safe, patient-centered, effective, timely, efficient, and equitable. Such care must be provided with technical competence and cultural sensitivity and must foster patient choice based on informed decision making. NCI research supports the development and dissemination of quality improvement interventions and methods to measure their success in improving health-related outcomes across the cancer continuum. To address the third objective, Improving the Quality of Life for Cancer Patients, Survivors, and Their Families, the NCI supports research on the development and dissemination of interventions to reduce the adverse effects of cancer diagnosis and treatment and to improve health-related outcomes for cancer patients, survivors, and their families/caregivers. Finally, the fourth objective, Overcoming Cancer Health Disparities, focuses on the best opportunities to lessen the burden of cancer for all. The NCI's investments are speeding the development and use of interventions to combat disparities across the cancer control continuum and among all underserved populations. The NCI supports research to identify factors contributing to disparities, to develop culturally appropriate approaches, and to disseminate interventions to overcome those disparities across the cancer control continuum from disease prevention to end-of-life care.

The NCI staff participate in multiple, diverse scientific partnerships and collaborative activities with other federal and non-federal scientists that benefit women as well as men and children. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, the NCI staff take advantage of opportunities to accelerate the pace of discovery and facilitate the translation of research knowledge into clinical application. The following are examples of such activities.

The NCI Community Cancer Centers Program (NCCCP)

The NCI is launching the NCCCP in early 2007 as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multispecialty care to a much larger population of patients. The NCCCP complements other NCI initiatives to draw more patients into clinical trials in community-based settings; reduce health care disparities; prepare sites for standardizing the collection and storage of biological specimens for cancer research; link sites to national databases supporting basic, clinical, and population-based cancer research; and implement electronic medical records. Pilot sites will also share best practices and refine the overall concept as a prelude to launching a national network of research-driven cancer care at the community level.

Centers for Transdisciplinary Research on Energetics and Cancer (TREC)

The TREC centers have been developed to foster collaboration among transdisciplinary teams of scientists to accelerate progress to reduce cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. This program is part of the NCI's larger energy balance research focus, complementing the trans-NIH Obesity Task Force.

Cancer Intervention and Surveillance Modeling Network (CISNET)

The CISNET is a consortium of NCI-sponsored teams that use biostatistical modeling to improve understanding of cancer control interventions in prevention, screening, and treatment. The teams use data from randomized controlled trials, meta-analyses, observational studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions. Currently CISNET has teams focusing on breast, prostate, colorectal, and lung cancers.

Nanotechnology Alliance for Cancer

This alliance has begun harnessing nanotechnologies for cancer diagnostics, targeted imaging, and drug delivery. Multifunctional, targeted devices capable of bypassing biological barriers will enhance our ability to treat cancer effectively and efficiently by delivering therapeutic agents directly to cancer cells.

The caBIG™ (cancer Biomedical Informatics Grid™)

This initiative was launched to make information easier to share by connecting scientists and practitioners through a shareable and interoperable infrastructure that has standard rules and a common language. caBIG™ will build or adapt tools for collecting, analyzing, integrating, and disseminating information associated with cancer research and care.

The Cancer Genome Atlas (TCGA)

The TCGA is a pilot project to assess the feasibility of a full-scale effort to systematically identify all genetic changes involved in human cancer. Investigators will study lung, brain (glioblastoma), and ovarian tumors. All data will be publicly available to researchers worldwide through caBIG™.

The NCI educates cancer patients, health and research professionals, and the public about women's health and cancer research in a variety of formats. Information is provided to the public, the cancer community, and journalists through the NCI Web site at http://www.cancer.gov/. The NCI's Research on Cancers in Women Web page provides highlights

of NCI-supported research to understand, prevent, diagnose, and treat cancers in women at http://women.cancer.gov/. Cancer information is also provided through staffed NCI exhibits at key conferences, meetings, and events. The NCI Cancer Information Service (CIS) shares information about cancer prevention, risk factors, symptoms, diagnosis, treatment, research, and smoking cessation. CIS information specialists provide the latest, most accurate information about cancer by telephone (1-800-4-CANCER) and on the Internet through LiveHelp instant messaging service on NCI's Web site (http://www.cancer.gov/). CIS also provides printed and electronic NCI publications through the NCI Pubs Locator available online at https://cissecure.nci.nih.gov/ncipubs/ or by calling 1-800-4-CANCER. Through its Partnership Program, 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.

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 P.L.105-277, which was signed by the President in October 1998. The mission of the NCCAM is to explore complementary and alternative healing practices in the context of rigorous science, train CAM researchers, and 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 interventions proven to be safe and effective become accepted as mainstream health care practices. The NCCAM groups CAM practices within the following areas: (1) whole medical systems (i.e., traditional Chinese medicine, naturopathic medicine, Ayurveda); (2) mind-body medicine (i.e., meditation, yoga); (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). The NCCAM conducts and supports basic and applied (clinical) research and research training within these areas.

The 2002 National Health Interview Survey (NHIS) 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, the most prevalent CAM practice, was excluded from the definition of CAM, more than a third (36 percent) still reported use of CAM in the previous 12 months. 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 CVD. CAM therapies for women treat a variety of conditions, such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and reproductive issues. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions. During FY 2005 and 2006, NCCAM's Senior Advisor for Women's Health served as a coordinator for women's health activities and a liaison to the NIH Office of Research on Women's Health.

National Center for Research Resources

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support enables discoveries that begin

at a molecular and cellular level to move to animal-based studies and on to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. The NCRR connects researchers with one another as well as with patients and communities across the nation to harness the power of shared resources and research. The NCRR develops and supports biomedical resources that include sophisticated 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, state-of-the-art equipment available on a shared basis, strong research infrastructure for predominantly minority institutions, infrastructure enhancement and mentorship at institutions in states with little history of NIH funding, and 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 to address emerging clinical and basic research needs. The NCRR is leading a national consortium—funded through Clinical and Translational Science Awards—that will transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients.

The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by the NCRR to promote understanding of normal and abnormal physiology in women. In addition, the NCRR supports research on the prevention and treatment of diseases, disorders, or conditions that are unique to women or have a significant impact on women. Accomplishments highlighted below 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 esearch 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 multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. 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 supports the Research Infrastructure in Minority Institutions Program (RIMI) and the Minority Health and Health Disparities International Research Training Program (MHIRT). These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities for the benefit all affected populations, including women of diverse populations.

The NCMHD Loan Repayment Program

The NCMHD has two distinct loan repayment programs: 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 the Extramural Clinical Research Program, which supports the recruitment and retention of health professionals from disadvantaged backgrounds to conduct clinical research.

The NCMHD Centers of Excellence Program

This program funds Centers of Excellence that conduct research, research training, and community outreach activities relevant to health disparities. These centers advance the science

related to health disparities; create, develop and evaluate new interventions for preventing, reducing, and eliminating health disparities; and disseminate to health disparity communities information useful for improving health.

The NCMHD Research Endowment Program

This program builds research and training capacity in institutions that significantly invest 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.

The NCMHD Research Infrastructure in Minority Institutions Program (RIMI)

This program helps institutions that enroll a significant number of students from minority health disparity populations develop and enhance their capacity and their competitiveness to conduct biomedical research. The RIMI program also assists non-doctoral degree institutions in developing their research infrastructure, primarily through collaborations with research-intensive universities.

The NCMHD Minority Health and Health Disparities International Research Training (MHIRT) Program

This program enables U.S. institutions to offer qualified eligible students in basic, biomedical, clinical, or behavioral science short-term, international research training opportunities that 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, a five-year strategy and accompanying budget that guides the NIH research agenda for combating health disparities. In FY 2004, the NIH Committee on Minority Health and Health Disparities Research Definitions and Application Methodology developed a new definition for minority health and health disparities and consistent guidelines. The NIH ICs will use this guidance, which now includes low socio-economic status and rural populations, when reporting on minority health and health disparities activities.

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 (i.e., glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer on average than men, more women than men are affected by these age-related eye diseases in the U.S.

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 and in most cases 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 from age or trauma; 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 global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases and to enhance the health of all individuals so that they can live longer and more fulfilling lives. To achieve this vision, the NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and government agencies. The NHLBI collaborates with patients, families, health-care professionals, scientists, professional societies, patient-advocacy groups, community organizations, and the media to maximize the use of research results and leverage resources to address the public health needs of the nation. All activities of the NHLBI are carried out in a spirit of public service and with a commitment to excellence, innovation, integrity, respect, compassion, and open communication.

The NHLBI places high priority on improving the cardiovascular health of women by supporting fundamental and clinical research to elucidate the role of sex hormones in cardiovascular health, identify and enhance healthy behaviors, and develop methods and practices for prevention, diagnosis, and treatment. Its research programs have generated important new knowledge about the influences of lifestyle, menopause, chest pain, hypertension, diabetes, and drug treatment (including hormone therapy) in women and also have led to improved diagnostic tests and treatment guidelines for women. In particular, the NIH Women's Heath Initiative, which is administered by the NHLBI, and the NHLBI Women's Ischemia Syndrome Evaluation have yielded invaluable scientific advances. The former continues to provide sex-specific data regarding women's cardiovascular health, cancer, and osteoporosis and is now making available its rich resources to seed new investigations that address women's health needs. The latter is nearing completion of its second project period and plans to compete for additional funding to test and validate innovative diagnostic tools and further explore the pathophysiology of chest pain and non-obstructive coronary ischemia, a condition prevalent in women. The Heart Truth, the NHLBI national awareness campaign for women about heart disease, continues to flourish, extending the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease. The NHLBI Center for the Application of Research Discoveries, formerly the Office of Prevention, Education, and Control, has responsibility for The Heart Truth.

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 it has already begun to change the way we address research on women's health.

In October 2005, a different international consortium of dedicated scientists from six countries, again led by the NHGRI, announced the production of a very different map of the human genome, one that may prove even more powerful because of its medical applications. The result is the "HapMap." Like the earlier sequence, all of the data from the HapMap has been placed in the public domain. The HPG spelled out the letters of the DNA code that all human beings share. The HapMap provides detailed information about the variation in the genome. The HapMap investigates those spelling differences in the human instruction book that predispose some people to different types of cancer as well as other diseases. In December 2006, the NHGRI awarded a contract to continue the HapMap Project to make it an even more powerful tool to reveal the way in which genetic variation is organized into chromosomal neighborhoods. As this information unfolds, the NHGRI will

continue to investigate diseases specific to women.

In 1994, NHGRI investigators were among the first to report that women carrying the gene mutations called Breast Cancer 1 (BRCA1) or Breast Cancer 2 (BRCA2) have a higher risk of developing both breast and ovarian cancer than women without such mutations. The NHGRI continues to investigate the role of these genes in breast and ovarian cancer, and this research has led to better screening and treatment of those with a family history of breast cancer. In hopes of expanding the usefulness of this research, the NHGRI also supports research that explores the effect of educating women of different ages and ethnic group about benefits of genetic screening in evaluating their risk of inherited diseases.

National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) funds basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses that affect the health of women and girls. The NIAID involves women in many of its clinical studies on the treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). The NIAID also collaborates with other organizations on research initiatives aimed at improving women's health.

The Institute's report provides an overview of recent accomplishments and initiatives in women's health research. These accomplishments include the expansion of the Autoimmunity Centers of Excellence, the Immune Tolerance Network, and the Autoimmune Disease Prevention Centers; the Phase II/III PRO 2000/5 Gel and Buffer Gel microbicide trials; the sequencing of the Trichomonas vaginalis genome; and the Phase III clinical efficacy trial of an investigational vaccine for genital herpes, known as the Herpevac Trial for Women. Other initiatives and programs covered in this summary include the Women's HIV Interagency HIV Study, the Center for AIDS Research's Women's Health Supplement, the Microbicides Trials Network, and the HIV Prevention Trial Network conducted in the U.S. and overseas.

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 that disproportionately affect women including osteoarthritis, osteoporosis, rheumatoid arthritis, TMJD, fibromyalgia, scleroderma, and systemic lupus erythematosus (lupus). Scleroderma and lupus are diseases in which health disparities have been clearly identified. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

At present, therapies available to treat osteoarthritis are limited. Drug therapies target the symptoms but not the causes of this disease. No treatment inhibits the degenerative structural changes that are responsible for its progression. To further facilitate the development of improved diagnostics and treatments for osteoarthritis, the NIAMS continues to support the Osteoarthritis Initiative (OAI). The first data set from this public-private partnership was recently released and is available to researchers worldwide. Information from the OAI will help to expedite the pace of scientific studies and allow investigators to identify potential new disease targets and develop tools for understanding how to measure clinically meaningful improvements.

Using data from the NIH Women's Health Initiative Observational Study, researchers have found that postmenopausal breast cancer survivors may be at increased risk for bone fractures associated with osteoporosis. Other NIAMS-supported researchers have located

a gene that not only influences bone density in mice, but this research also provides new insights into how to preserve bone mass in people. The gene, Alox15, had previously only been linked to fat metabolism and heart disease. This research holds tremendous promise for expanding understanding of the disease and ultimately preventing or slowing disease progression.

Results from a study supported by the NIAMS, the NIH ORWH, and the National Institute of Occupational Safety and Health (NIOSH, part of the Centers for Disease Control and Prevention) have broadened our understanding of the effectiveness of surgical versus non-surgical interventions for treating low back pain. Low back pain is one of the most common and frequently debilitating musculoskeletal conditions. In this study, after two years, improvements in levels of reported pain were seen in all patients regardless of their assignment to treatment protocol. However, patients receiving surgery reported having the highest level of improvement across both groups. This information will allow patients and their health care providers to select a treatment intervention based on their preferences.

In recent years, research has led to a new understanding of rheumatoid arthritis and has increased the likelihood that, with time, scientists will find even better ways to treat the disease. Several genetic and molecular components have recently been identified that may prove to be useful therapeutic targets. To better understand the genetic components of this disease, NIAMS-supported researchers examined the genes of identical twins—one with and one without rheumatoid arthritis. Three genes were identified as being overexpressed in patients with rheumatoid arthritis. These findings are exciting because they offer new insights into the mechanisms by which rheumatoid arthritis is mediated.

One of the greatest tools for researchers trying to understand a disease and test treatments for it is to have a mouse strain that develops problems similar to those of people with the disease. Researchers have used this approach to examine the skin thickening that occurs in patients with scleroderma. Results indicated that a chemical messenger plays a key role in this process. Such information will help scientists design therapeutic strategies for preventing this type of tissue damage associated with scleroderma.

For most people, discomfort from TMJD and muscle disorders will eventually go away with little or no treatment. Some, however, develop significant, long-term problems. Researchers studying a model of TMJD have found that reduced expression of a protein that lubricates the jaw is associated with cartilage damage and could cause joint degeneration. Further investigation revealed that interactions between this protein and certain growth factors could provide additional insight into the development of new, targeted treatments.

Lupus is a complex autoimmune disease, and its cause is unknown. It is likely that a combination of genetic, environmental, and possibly hormonal factors work together to cause the disease. Some lupus treatments lead to early and severe effects of menopause that can contribute to emotional and physical dysfunction. Results of a study supported by the NIAMS indicated that women with lupus may experience the benefits of postmenopausal hormone therapy without an increased risk of severe disease flares. Traditionally, doctors have not prescribed hormone therapy in women with lupus for fear that increasing the level of female hormones in the body might increase disease activity. Additionally, Epstein-Barr virus (EBV) has often been suspected as a trigger for lupus, but recent research has yielded a more direct association. These results provide insights into how the disease begins and have implications for how to treat or even prevent the disease.

NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest research institute within the National Institutes of Health (NIH). It was established by law in December 2000. The NIBIB received its first appropriation and grant-funding authority in 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 the 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 for 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 FY 2005 and 2006, the NIBIB funded grants 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, such as osteoporosis. 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 FY 2005 and 2006, the NIBIB supported research on women's health in the following disease areas: aging, autoimmune disease, breast cancer, cervical cancer, reproduction, diabetes-related research, obesity, epilepsy, HIV/AIDS, heart disease, osteoporosis, and TMJD.

Dr. Roderic Pettigrew, the first Director of the NIBIB, began his tenure at the NIH in September 2002. Since his arrival, the NIBIB has reorganized the Institute to facilitate the support of interdisciplinary 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 and subsequently of the Office of Research Administration. Under his purview, Dr. Demsey has responsibility for managing and monitoring all the NIBIB activities that specifically focus on women's health research. In February 2007, Dr. Valery Gordon (formerly of the Office of the NIH Director, Office of Extramural Research) joined the NIBIB and will have responsibility for women's health research oversight. In addition, Drs. Demsey and Gordon direct the efforts of the NIBIB to support research on women's health by serving as the NIBIB representatives to the Coordinating Committee on Research on Women's Health of the NIH Office of Research on Women's Health (ORWH).

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. Part of the Institute's mission is dedicated to ensuring that babies are born wanted, timely, and healthy and that they develop to their full physical, emotional, and cognitive potentials. To achieve this mission, the NICHD sponsors research that spans human growth and development, starting from before conception and continuing through infancy, childhood, and adolescence—all critical stages where the foundations for adult health and healthy women are established. Given its mission, the Institute's research aims to overcome many of the complex challenges that face women in addition to those faced by their children and families.

For instance, NICHD-supported research is shedding light on the role that certain genes play in forming fibroids, providing scientists with the preliminary knowledge that they need to begin developing new treatments. In another study, NICHD scientists identified the imbalance of molecules in blood that may be used to predict preeclampsia in pregnant women, a complication that can be fatal. The Institute is also supporting research that has

shown a link between the development of endometriosis and the level of environmental chemicals.

The NICHD's advances in women's health are as wide-ranging as the Institute's portfolio, which includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are critical to improving the quality of life for women. Highlighted in the Institute's report are just some of the most recent and significant research activities related to women's health.

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 and infectious 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 diseases, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone diseases; salivary gland dysfunction and disease; craniofacial birth defects and developmental disorders; and connective tissue diseases and disorders.

The NIDCR has a long tradition of support and leadership in the field of pain research. The Institute's work in pain research includes conditions where gender-based differences have been reported, such as TMJD. Researchers have found that the prevalence of back pain, headache, and pain associated with TMJDs increases significantly with increasing pubertal development in girls, but only back pain increased significantly in boys. Thus, for girls, pubertal development was a better predictor of pain than age. During FY 2006, the NIDCR funded the first, large, prospective clinical study to identify risk factors that contribute to the development of temporomandibular joint (TMJ) disorder. That study, the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), will open a critical and largely unexplored window on the early stages of the disorder, pointing researchers toward possible targets for better treatments to control pain.

The NIDCR's commitment to the fundamental study of the body's hard tissues, such as 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. Among the NIDCR's efforts in this area are studies that are characterizing the TMJ disk at tissue and cellular levels, thus providing vital information that will one day allow for biological approaches to reconstruct or regenerate the temporomandibular joint.

Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the Institute has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. Genetic studies on the area of pain include the haplotype mapping of catechol-O-methyltransferase (COMT) and responses to specific pain-evoking stimuli. Three common haplotypes in the COMT gene have been identified, and they relate to the threshold and tolerance to thermal, ischemic, and mechanical stimuli and temporal summation to heat pain.

The association between periodontal diseases and systemic effects continues to be a high priority for the NIDCR. For example, the NIDCR is supporting clinical trials on maternal periodontal infections and whether or not they represent a bona fide risk factor for preterm birth and growth restriction. Other evidence suggests that periodontal disease and its progression may represent an infectious and inflammatory exposure that could have serious deleterious effects during pregnancy. The NIDCR sponsored two large, randomized trials designed to determine if non-surgical treatment of periodontal disease during pregnancy reduced the incidence of preterm birth and associated growth restriction. Both the Obstetrics and Periodontal Therapy (OPT) trial and the Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) trial were designed

to determine whether pregnant women having non-surgical periodontal therapy during the second trimester of pregnancy had fewer premature and/or low-birth weight infants when compared with women having periodontal therapy after delivery. Results from the OPT trial were published recently in the *New England Journal of Medicine* and indicate that pregnant women who received non-surgical treatment for their periodontal disease did not lower significantly their risk of delivering a premature or low birth-weight baby. Non-surgical or standard periodontal treatment involves thoroughly cleaning of the teeth above and below the gums, commonly called scaling and root planning. This study also evaluated the safety of general dental care during pregnancy. It found that dental treatment through the second trimester—both general and periodontal care—did not increase the number of adverse events for women during pregnancy. However, for the first time, the safety of providing periodontal care to women in their second trimester was established.

Overall, research advances that affect women in particular are to be found within many of the Institute's broad research categories. The Institute's report highlights the accomplishments and initiatives in the areas of chronic pain, temporomandibular disorders, osteoporosis and basic bone biology, 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 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; IBS and other functional gastrointestinal disorders; osteoporosis; thyroid diseases (including Graves disease, goiter, and hypothyroidism); hyperparathyroidism; gallstones; primary biliary cirrhosis; painful bladder syndrome/interstitial cystitis; urinary tract infections; urinary incontinence; and lupus nephritis, the kidney disease of systemic lupus erythematosus. Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as hormonal factors in breast cancer and the relationship of obesity to CVD. 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 2005 and 2006, the Institute has made progress in the following areas important to women's health, which is highlighted in the Institute's report: prevention and treatment of diabetes and its complications, osteoporosis, irritable bowel syndrome and other functional gastrointestinal disorders, liver disease research, obesity and nutrition, kidney disease, PBS/IC, urinary tract infections, and urinary incontinence. The ORWH has worked with the NIDDK to foster research in many of these areas.

National Institute of Environmental Health Sciences

Environmental agents are likely to play a role in a number of important disease that predominantly affect females, including breast cancer, osteoporosis, ovarian dysfunction, 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 in their etiology, to identify important environmental triggers for their development and important nutritional factors that can reduce risk, and to deter-

mine 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.

The NIEHS has several groups focused on women's health. The Laboratory of Reproductive and Developmental Toxicology conducts basic research underlying important toxicological principles in the context of reproductive and developmental health. A major goal of the Hormones and Cancer Group is to understand how steroid hormones regulate growth and contribute to oncogenesis in target organs, such as the uterus and mammary gland. The Chromatin and Gene Expression Group has a strong interest in the epigenetic regulation of the human breast cancer susceptibility gene BRCA1, the IKK promoter and the estrogen-regulated cathepsin D, a protease whose overexpression is closely associated with a poor clinical outcome for patients with breast cancer. Dr. Donna Baird is a reproductive epidemiologist at NIEHS. Her research is focused on fertility, early pregnancy, and epidemiology of uterine fibroids. The NIEHS Comparative Pathobiology Group is studying the pathogenesis/carcinogenesis of tumors that affect the reproductive tract of rodents and humans and assessing the role of environmental and endogenous hormonal factors in the growth of these tumors. By understanding the basic mechanisms of disease, therapeutic interventions can be developed that will help spawn alternative, non-invasive treatments for clinical fibroids and other 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. For example, 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 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. Accomplishments in this area are described in the Institute's report.

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 and eating disorders than boys, while boys are more likely to suffer from autism and attention deficit disorder. 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, some women are at increased risk of depression during certain times of reproductive change, such as during the perinatal period.

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. To achieve this goal, the NIMH has offices and groups designated to focus on women's mental health. The Women's Mental Health Program is located in the Office for Special Populations within the Office of the NIMH Director. The women's mental health program 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 the liaison with the NIH ORWH 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. This Office coordinates NIMH activities that 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 the NIMH scientific activities related to women's health and sex/gender differences research. Members of the team include representatives from all five extramural research divisions and the Offices of Science Policy, Planning and Communications, Constituency Relations and Public Liaison, and the Executive Office. Team member's work across disciplinary boundaries to plan workshops, prepare and review science reports, and create program announcements related to women's mental health.

In addition to increasing scientific information on sex and gender differences, the NIMH has advanced knowledge in the area of specific mental disorders that either affect women exclusively (e.g., perinatal depression) or predominantly (e.g., eating disorders). Through cross-cutting programs, such as the Women's Mental Health Team, the NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and the prevention of mental disorders in women. The Institute's report highlights accomplishments, papers on sex differences and women's mental health research, specific initiatives to promote research in this area, efforts on behalf of special populations of women, as well as specific initiatives in the area of sex/gender differences research. Research highlights are grouped by three major subheadings: Research on Sex Differences in Brain and Behavior, Research on Specific Mental Disorders, and Research on AIDS and Mental Health Disparities.

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, every segment of society, and 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, epilepsy, and Rett syndrome. The NINDS supports basic, translational, and clinical research on these and other neurological disorders. While research on women's health is found across the NINDS portfolio, the Institute designates one staff member from the Division of Extramural Research as its representative to the NIH 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 (MS) is a chronic autoimmune disease of the central nervous system that causes inflammation and the loss of myelin, a protective covering around 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 impairment. Several disease courses are possible. About 10 percent of patients experience a primary progressive form of MS, where the disease worsens continuously. The relapsing-remitting type of MS, where episodes of worsening neurological function alternate with periods of partial or complete recovery, affects 85 percent of patients. Hormonal factors may influence MS; some forms of MS are about two-fold more frequent in women, and fewer relapses are reported during pregnancy. The NINDS supports research on the mechanisms of MS and other autoimmune disorders, as well as clinical and translational studies aimed at developing new therapeutic approaches to MS.

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 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, mechanisms of pain processing, modulation, and regulation, and pain management.

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 U.S. and a major cause of disability in both women and men. In general, women have a lower risk of stroke than men. However, 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 to 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.

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 others, 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. The NINDS supports a broad portfolio of basic, translational, and clinical studies of epilepsy and epileptogenesis. In addition, the NINDS funds the Anticonvulsant Screening Program (ASP), a drug discovery program focused on epilepsy and other closely related neurological disorders.

Rett syndrome is a childhood neurological impairment seen almost exclusively in females. Rett syndrome is characterized by severe cognitive impairment, autistic behavior, stereotypic movements, and frequently seizures. The disease is associated with mutations in a gene called MECP2, located on the X chromosome, that lead to an insufficient amount or abnormal function of the MECP2 protein. The NINDS supports research aimed at understanding the mechanisms of action of the MECP2 protein and at developing new potential therapies.

NATIONAL INSTITUTE OF NURSING RESEARCH

The mission of the National Institute of Nursing Research (NINR) is to support clinical and basic research that establishes a scientific basis for the care of individuals across the life span. NINR-supported research encompasses the health of individuals, their families, and their caregivers. It also focuses on the special needs of at-risk and underserved populations, with an emphasis on health disparities. The Institute's research focus transcends many disciplines to promote health and improve patient and caregiver quality of life across a broad range of diseases and conditions. The NINR unites the disciplines of biological and behavioral sciences to elucidate the complex interactions between the physiological factors of health and disease and the behavior, decisions, and perceptions of the individual. Taken together, the elements of the NINR's mission shape a forward-looking research agenda whose relevance is underscored by today's health care challenges and opportunities.

In 2006, the NINR released its new five-year strategic plan, titled Changing Practice, Changing Lives. Developed in close consultation with representatives of the extramural community, this new plan details the NINR's scientific priorities. The Institute will focus its research on health promotion and disease prevention; improving quality of life through self-management, symptom management, and caregiving; eliminating health disparities; and leading critical research on the end of life. The plan also highlights four cross-cutting strate-

gies for advancing nursing science, including advancing the integration of biological and behavioral sciences, promoting the design and use of new patient care technologies, improving nursing science methods, and developing the next generation of investigators. The full text of the strategic plan elaborates on each of these areas and can be found on the NINR's Web site at www.ninr.nih.gov/.

The NINR's mission and research goals are inherently suited to addressing the current challenges in women's health research. NINR-supported investigators have made numerous key findings during FY 2005 and 2006, further advancing our understanding of the many issues uniquely relevant to women. These areas include improving maternal and perinatal health, aging, cardiovascular health, pain management, and HIV/AIDS prevention and treatment. The NINR also sponsors or co-sponsors a number of research initiatives on topics related to women's health, including pain research, chronic fatigue syndrome, improving care for dying children, and increasing the participation of women in clinical trials.

The elimination of health disparities is a critical cross-cutting area of research throughout the field of women's health, and this is certainly true at the NINR. Consistent with its strategic goal of supporting research into the causes of health disparities and finding ways to overcome them, the NINR maintains a robust research portfolio that studies the disparities experienced by women in minority, rural, and other underserved populations. In FY 2005 and 2006, NINR investigators made strong gains in these areas, including designing ways to improve social support among chronically ill women in rural areas, promoting mammography screening among black women, developing a mental health intervention to decrease depression among single mothers, and improving knowledge of HIV prevention among Latinas.

The NINR is committed to improving clinical practice through the generation of new knowledge and the development of leaders in nursing science. Today's challenges in the field of women's health present unprecedented opportunities for the Institute to further expand its impact on the health of the nation. By focusing on the areas of research outlined in its strategic plan, areas which are aligned with critical public health needs, the NINR will ensure that these challenges are proactively addressed.

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 of Alzheimer's disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2005 and 2006, NIA-supported researchers made important progress in a number of women's health-related areas.

For example, ongoing research related to Alzheimer's disease is looking at the effects of menopausal hormone therapy on cognition. Mechanisms through which estrogen and related hormones work on the brain continue to be elucidated. Another recent study demonstrated that the elevated levels of follicle stimulating hormone (FSH) seen in menopausal women may play a key role in bone loss and the development of osteoporosis. Research continues on the etiology and predictors of hot flashes in women around the time of menopause, as well as other symptoms that may accompany the menopausal transition, such as sleep problems and joint pain. NIA-supported investigators continue to explore the reasons behind gender differences in disability, morbidity, and mortality at older ages.

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 and ethnic backgrounds.

Women's Health Initiative Study of Cognitive Aging (WHISCA)

The WHISCA is an ancillary project of the Women's Health Initiative Memory Study

(WHIMS) and the Women's Health Initiative (WHI), a randomized clinical trial of menopausal hormonal therapy. Since 1999, WHISCA has investigated the effects of menopausal hormonal therapy on longitudinal changes in memory and specific cognitive functions in older non-demented WHI participants.

Women's Health and Aging Study (WHAS)

WHAS I and II are major studies of the etiology of disability in older women. Although recruitment has ended, data analysis and reporting continue.

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 NIA also supported major workshops on women's health-related topics in FY 2005 and 2006. Of note was a state-of-the-science conference on the management of menopausal symptoms.

Older women outnumber older men in the U.S., and the proportion of the population that is female increases with age. In 2003, according to government statistics, women accounted for 58 percent of the population age 65 and over and for 69 percent of the population age 85 and older. 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 hip fracture; physical disability; caregiver burden (research has shown that caregivers are more likely to be women); decline in function in older women; age-related muscle loss; and cancer in older women. The Institute has a Women's Health Coordinator in the Office of Planning, Analysis, and Evaluation who coordinates NIA activities related to women's health and serves as the liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and planned research initiatives aimed at women, are described in the Institute's report.

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. It is estimated that there are 18 million alcohol-abusing or alcohol-dependent individuals in the United States, of which more than four 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's health. Research related to women's health is found in each programmatic division of the Institute. Because of the multidimensional and multidisciplinary nature of alcohol use disorders and their prevalence worldwide, collaborative research endeavors on a national and international scale are required for progress toward the goals of reducing alcohol abuse disorders and alcoholism among women. Significant scientific advances in understanding the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women have occurred in the past two fiscal years. This report addresses research on women and alcohol along six central themes: (1) epidemiology of women's drinking; (2) gender differences; (3) alcohol and pregnancy; (4) alcohol use and fetal alcohol spectrum disorders; (5) treatment of women with alcohol use disorders; and (6) violence and other social consequences of alcohol abuse. In addition, chronic fatigue syndrome (CFS), a disorder predominantly of women, in the context of alcohol use disorders is a new area of focus for the Institute.

Trends in heavy drinking among women continue to decline with increasing age, as does overall drinking, mirroring trends in the general population. However, patterns of drinking (quantity/frequency) indicate that binge drinking, particularly among younger women, is problematic. Women are more susceptible than men to the adverse consequences of alcohol. Furthermore alcohol affects men and women infected with the hepatitis C virus (HCV) differently. Epidemiologic studies provide evidence that heavy drinking contributes to HCV-related disease progression and death. Heavy-drinking, HCV-infected women died more than a decade earlier than HCV-infected women who drank only moderately or not at all. Women with HCV who drink heavily squander their normal survival advantage over men with the same infection.

Preclinical studies in animal models have begun to reveal the mechanistic basis underlying gender differences in alcohol-induced organ damage. Studies of alcoholic liver disease have shown that alcohol increases the activity of inflammatory proteins within the liver, an effect that is modulated differently by estrogen or testosterone. Female rats had a heightened inflammatory response compared with male rats, which could, in part, account for their enhanced susceptibility to liver damage. Chronic ethanol (alcohol) abuse is correlated with osteoporosis. Hormonal supplementation with estradiol seems to afford a measure of protection against ethanol-induced bone loss in female rats, perhaps by augmenting the activity of bone forming cells.

Research has firmly established that maternal alcohol consumption can lead to fetal alcohol syndrome (FAS), the leading preventable cause of mental retardation. A study conducted in several urban and rural communities in South Africa in mothers of grade school children with FAS confirmed that drinking before, during, and after pregnancy was associated with lower IQ and behavioral problems in their children. The NIAAA support for the Collaborative Initiative on FAS and fetal alcohol spectrum disorders (FASD) is expected to lead to new insight into the underlying mechanisms of these disorders and development of therapeutic interventions to provide relief to those affected with the most debilitating features of the disease. Multiple international sites with a high incidence of FAS and FASD are participating in this important study, including a cooperative agreement with the Moscow Region Ministry of Health to screen more than 26,000 pregnant women and select a sample of offspring for longitudinal follow-up. A cooperative agreement was established jointly with the NICHD to conduct community-linked studies to determine the underlying causes of sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and FASD, and the role of prenatal alcohol exposure. The long-term goals of this initiative are to decrease fetal and infant mortality and to improve child health in the affected communities.

Identification of women at risk for children with FASD has been challenging. T-ACE (Tolerance, Annoyed, Cut Down, Eye-Opener) was developed specifically to screen for alcohol problems in pregnant women and has been validated as more accurate and sensitive than previous instruments. Using the T-ACE instrument, investigators have shown that, contrary to what might be expected, social support during pregnancy was not predictive of subsequent prenatal alcohol use. Moreover, women's knowledge of healthy pregnancy habits had only a weak relationship with prenatal alcohol consumption. These results provide evidence that specific knowledge about the risks associated with prenatal drinking alone is insufficient to change behavior; therefore, universal screening of all pregnant women is recommended. Screening to reduce risky drinking among non-pregnant women of childbearing age may also be advisable as a way to identify women in this age group who would benefit from counseling.

Alcohol abuse in risky environments is associated with women's ability to make and effect decisions regarding their health and welfare, such as the right to refuse unsafe sexual practices. A recent study shows that alcohol consumption increases consent; however, assertive resistance increases as the level of sexual aggression escalated. Even at a relatively high level of alcohol consumption, a woman can understand the threatening nature of the situation. Childhood trauma was a major predictor of vulnerability to sexual assault. An ongoing randomized clinical trial is focus-

ing on reducing HIV risk behaviors among women seeking help for alcohol problems. It is anticipated that women who respond favorably to alcohol treatment and who receive 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 receiving standard risk reduction interventions.

In summary, scientific research continued in FY 2005 and 2006 on gender-based differences in the causes, consequences, prevention, and treatment of alcohol use disorders. A new area of research emerged, involving a partnering between the NIAAA and the ORWH on CFS. One initiative focused on the epidemiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the life span. The objective of a second initiative was to elucidate the interactions of neural and immune systems in the CFS disease process and to determine how alterations in physiological systems affect the progression and manifestation of CFS. The NIAAA, the NIDA, and the SAMHSA co-sponsored a conference on women, addiction, and recovery. The conference was designed to advance the field of women's substance abuse treatment by presenting the latest research and discussing how it can be applied to improve clinical practice and service delivery for women with substance use disorders. Ultimately, long-term structural changes in women's social status in the effort to reduce maladaptive behavioral strategies including alcohol consumption and alcoholism, and their biomedical and behavioral consequences are needed.

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 is 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 are detailed in the Institute's report.

NATIONAL INSTITUTE ON DRUG ABUSE

As the foremost authority on drug abuse and addiction, sponsoring the vast majority of the world's research on the subject, science supported by the National Institute on Drug Abuse (NIDA) addresses the most fundamental and essential questions about drug abuse. The Institute does this by monitoring emerging trends, identifying and studying underlying physiological and social factors, and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within this science is a major effort to investigate issues specific to women and to study sex/gender differences.

Research in this area underscores the complexity of the relationship between drug use and sex/gender and biological vulnerability. Growing evidence suggests that for females, drug abuse may begin and progress differently; is characterized by different risk and protective factors, and motivations; and has different consequences. In recognition of the important role that sex/gender plays in drug abuse, NIDA has strongly supported research to identify sex/gender differences and specific sex/gender aspects of drug abuse and addiction—applying these findings to design, test, and implement more effective drug abuse prevention, treatment, and services for both males and females.

Our current knowledge base for understanding the individual characteristics of males and females is not equal. Historically excluded from substance abuse studies (until the 1990s) due to their childbearing potential

and to methodological issues associated with the menstrual cycle, women have not realized the benefits of some research findings affecting both treatment and prevention of drug abuse. Since 1994, when NIH published guidelines on including women and minorities as clinical research subjects, the number of reports being published on substance abuse treatment for women has increased annually—but more research needs to not only stratify results based on gender, but to also include gender as a fundamental consideration in the design of studies and interventions aimed at preventing and treating drug abuse.

Office of Dietary Supplements

The Office of Dietary Supplements (ODS) supports research to expand the evaluation of the role of dietary supplements in disease prevention and the reduction of risk factors associated with disease. In addition, the ODS supports research to further understanding of the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle.

The ODS supports research on a range of issues related to women's health. Included in the ODS research portfolio are projects on the following disease and conditions that affect women.

- *Breast Cancer:* The role of phytoestrogens and their relationship to inhibiting and/or promoting breast cancer is of high interest to the ODS. The ODS co-funds basic and observational research in this area with the NCI, the NIA, and the NCCAM.

- *Menopause:* The ODS co-funds basic and clinical studies in the area of CAM therapies for women's health and menopausal symptoms with the NCCAM. This includes a Botanical Research Center that is focused on women's health. Botanicals under study include black cohosh, red clover, and soy. The Botanical Research Center is charged with characterizing and standardizing plant extracts to be used in future clinical trials for the evaluation of effect on menopausal symptoms.

- *Reproductive Health:* The ODS co-funds two training grants on conditions affecting unborn children with the NHLBI and the FIC. Through a cooperative agreement, the ODS co-funds an international grant focused on agriculture, maternal-infant nutrition, and public health.

The ODS, in conjunction with ORWH, also sponsors a BIRCWH project at the University of California, Davis.

Office of Behavioral and Social Sciences Research

The Office of Behavioral and Social Sciences Research (OBSSR) opened officially on July 1, 1995. The U.S. Congress established the OBSSR in the Office of the Director (OD), NIH, in recognition of the key role that behavioral and social factors often play in illness and health. The mission of the OBSSR is to stimulate behavioral and social sciences research throughout the NIH and to integrate these areas of research more fully into others of the NIH health research enterprise, thereby improving our understanding, treatment, and prevention of disease.

Given its mission as an OD office to develop and support projects that generate interest among a range of NIH ICs, the OBSSR does not typically initiate programs that narrowly target specific diseases. The Office, however, does support some individual research projects that have clear relevance to women's health.

The Office supports research in the areas of mind, body and health, including several common chronic disorders such as chronic visceral and somatic pain syndromes, disorders of mood and affect, and addictive behaviors can be related to alterations in the neurobiology of the central stress system. The OBSSR is co-funding, with the NCCAM, the UCLA Center for Neurovisceral Sciences and Women's Health (CNS/WH), which has assembled a large number of clinical and basic investigators interested in mind/body interactions. The investigators at this center have a particular interest in the role of stress and sex-based differences in altering these interactions in health and disease.

The OBSSR also supports research on coronary heart disease (CHD), which is the leading cause of death and functional limitations among women in the U.S. In collaboration with the NHLBI, the OBSSR is funding research to address the poorly understood natural history of long-term maintenance of change in multiple behaviors (i.e., dietary behaviors, physical activity, and stress management) related to CHD risk. In addition, research is studying the effects of theoretically important mediating variables on relapse and maintenance.

Adolescence represents a critical period for the development of overweight that tracks into adulthood. This risk is significantly heightened for teens who become pregnant and experience postpartum weight retention. Such weight gain can lead to impaired glucose tolerance, type 2 diabetes, and other diseases. The postpartum period offers a window of opportunity to modify eating and activity patterns associated with obesity. With the NCI, the OBSSR co-funds research to test Balance Adolescent Lifestyle Activities and Nutrition Choices for Energy (BALANCE), a multilevel intervention designed to reduce overweight in postpartum teens, as measured by change in body mass index (BMI).

Violence exposure among children and adolescents is a well-recognized problem, but it is usually conceptualized as either directly experienced or witnessed maltreatment occurring at the interpersonal or community level. In communities of color, this definition is inadequate because it does not take account of the multiple other sources of exogenous violence exposure. A study co-funded by the OBSSR and the NIMH examines the processes and mediators by which violence exposure may adversely affect young mothers of color and their children. It also documents the buffering or moderating effects of specific psychological resources.

Ovarian cancer is the second most common gynecologic cancer. Because of low rates of survival for the majority of ovarian cancer patients, identification of factors contributing to tumor growth and progression is of paramount importance. Although relationships between psychosocial factors and immunity have been extensively documented, there has been little investigation of relationships between psychosocial factors and cytokines involved in angiogenesis, the formation of new blood vessels that enhance tumor growth. A five-year prospective longitudinal study, co-funded by the OBSSR and the NCI, will investigate relationships among psychosocial factors and four angiogenic cytokines: VEGF, IL-6, IL-8, and IL-12. The study will include 154 ovarian cancer patients in a clinical setting. These cytokines are selected because of their critical role in ovarian cancer growth and progression.

OFFICE OF RARE DISEASES

The goals of the Office of Rare Diseases (ORD) are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have one of the approximately 7,000 rare diseases known today. The ORD collaborates with the NIH ICs and Offices to stimulate rare diseases research activities, foster collaboration with other entities nationally and internationally, and support activities in research, training, and outreach.

Since FY 2003, the ORD has collaborated with several NIH ICs, including the NCRR, NHLBI, NICHD, NIAMS, NIDDK, and NINDS, to support the Rare Diseases Clinical Research Network. The network consists of 10 consortia, each of which focuses on a group of rare diseases. In addition the network includes a data and technology coordinating center that serves all consortia.

Lymphangioleiomyomatosis (LAM) is one of the diseases under study in the Rare Lung Diseases Consortium. This disease affects almost exclusively women of childbearing age. Recently, a LAM protocol has been approved. The protocol, Multicenter International LAM Efficacy of Sirolimus (MILES) Trial, assesses the safety of Sirolimus administered orally or a placebo to assess the effect of Sirolimus on biological and clinical markers of lung function, including spirometry findings, dyspnea, quality of life, lung volume, diffusion, oxygenation, and exercise tolerance. The consortium expects to enroll 240 patients and 240 controls.

Rett syndrome (RTT) is a neurodevelopmental disorder that predominantly affects females and is characterized by severe cognitive impairment, autistic behavior, stereotypic movements, respiratory irregularities, and frequently

seizures. RTT is one of the three syndromes investigated in the Angelman, Rett, and Prader-Willi Syndromes Consortium. In 2006, the Rett Syndrome Natural History Clinical Protocol was approved, and the consortium has enrolled 479 research participants. The purpose of this protocol is to establish a phenotype-genotype correlation over a broad spectrum of Rett syndrome phenotypes including the longitudinal pattern of progression of clinical features, quality of life, and longevity across this cohort.

The Rare Genetic Steroid Disorders Consortium is an integrated international group of academic medical centers, patient support organizations, and clinical research resources. One of the diseases studied in the consortium include congenital adrenal hyperplasia (CAH), which can affect both boys and girls. CAH is a family of inherited disorders of the adrenal glands. Two CAH protocols relevant to women's health have recently been approved.

The ORD supported three conferences relevant to women's health on Rett syndrome, preeclampsia, and premature ovarian failure. In addition, the ORD supports, with the NHGRI, the Genetic and Rare Diseases Information Center (GARD). The GARD provides information to patients and their families, health professionals, researchers, and the public.

Office of AIDS Research

The Office of AIDS Research (OAR), located within the Office of the Director of the NIH, was established in 1988. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. This diverse basic, clinical, and behavioral research portfolio demands an unprecedented level of scientific coordination and management of research funds. The OAR coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, the OAR ensures that research dollars are invested in the highest priority areas of scientific opportunity. As such, the OAR represents the roadmap for NIH AIDS research, allowing NIH to pursue a united research front against the pandemic.

The OAR develops the annual comprehensive Trans-NIH Plan for HIV-Related Research. The plans for FY 2005 and 2006 were developed through the annual planning process established by the OAR to identify the most compelling scientific priorities to lead to better therapies and prevention strategies for HIV infection and AIDS. This plan for AIDS research establishes an agenda in the following areas of emphasis: vaccines; therapeutics; etiology and pathogenesis; natural history and epidemiology; behavioral and social science; training, infrastructure, and capacity building; and information dissemination. Research relevant to the needs of women is addressed in all of these areas.

To further enhance the area of microbicide research, the OAR provided key support for the 2006 International Microbicides Conference, which provided funding to allow scholarships for researchers from developing countries. The OAR announced a major new microbicide research initiative to enhance the NIH commitment to microbicide research, to better manage and coordinate the NIH microbicide portfolio, and to elevate the scientific priority and funding for this important area within the prevention research agenda. In addition, to catalyze efforts to address the priorities established in the strategic plan, the OAR provided funding for the Microbicides Innovation Program, a collaboration of the OAR, the ORWH, the NIAID, the NICHD, and the NIMH. The Microbicides Innovation Program funded 15 grants addressing pressing issues in microbicides development research.

At the recommendation of the OAR Advisory Council, the OAR established a Prevention Science Initiative to provide seed funds to jump-start innovative concepts in prevention research. The OAR provided pilot funds to supplement peer-reviewed projects submitted by the NIH ICs. The OAR supported a number of research projects that included components directed toward women. Among these were studies to integrate prenatal care to reduce HIV/STDs, to engage health care providers in female condom promotion, to synchronize HIV prevention strategies with HIV treatment guidelines, and to determine effectiveness of HIV interventions among women in developing countries.

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. In addition, the FIC and the ORWH have teamed up to explore issues facing women in science in developing countries and to consider gender and global health issues. These initiatives have informed the programmatic directions of the FIC and other NIH ICs.

Accomplishments

The FIC advances the NIH mission—making important medical discoveries that improve health and save lives—by facilitating medical discoveries that can improve health and save lives globally and by promoting the uptake of new discoveries at the individual, community, and national level, particularly in resource-limited settings worldwide. The FIC's research and research training programs address a wide range of topics of concern to the global health community, including infectious diseases, population dynamics, maternal and childhood conditions that contribute to maternal and infant mortality and morbidity, environmental and occupational health, bioethics, genetics, trauma and injury, tobacco control, and biodiversity.

Three of FIC's programs, the International Research and Training Program in Population and Health (POP), the International Maternal and Child Health Research and Training Program, and the AIDS International Training and Research (AITRP) Program, support a range of activities aimed at improving women's health. The program in population 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 program in maternal and child health, which was closed out in 2006, supported research training to address the continued high levels of maternal, perinatal, and infant mortality and morbidity in many countries. The AITRP 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 FIC's remaining programs have a much broader scope related to women's health issues. The Fogarty International Research Collaboration Award (FIRCA), a small grants program that fosters international research partnerships between NIH-supported scientists in the U.S. 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. The International Research Scientist Development Award (IRSDA), a mentored career development program, provides junior U.S. scientists with an opportunity to embark on or enhance their careers in research related to global health, and to prepare them for independent research careers. Examples of research supported by the IRSDA include family plan-

ning choices among HIV seropositive women, impact of HIV/papillomavirus co-infection, contextual correlates of HIV testing and pediatric vaccine trial acceptability. The Stigma and Global Health Research Program, which is co-supported by several other NIH Institutes and the ORWH, addresses the role of stigma in health and how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups, and societies worldwide. Some projects are specifically focused on linkages among 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 among youth in school.

The following are examples of selected projects supported by the FIC that focus on international issues in women's health and their outcomes.

HIV: Mother-to-Child Transmission

Reducing Mother-to-Child HIV Transmission (MTCT) in Rural Ugandan Populations

A single dose of nevirapine, the preventative regimen commonly self-administered by pregnant women at the onset of labor to protect against mother-to-child HIV transmission in resource poor countries, can only be administered to the newborns of HIV-positive mothers by health facility personnel. Since many women who live in rural areas do not deliver at health facilities, nevirapine coverage to the newborns of HIV-positive mothers living in rural areas is inadequate. Researchers at the Johns Hopkins Bloomberg School of Public Health and the Institute of Public Health at the Makerere University in Kampala, Uganda tested a new proof of concept assessing whether home-based newborn medication could improve coverage to both mothers and their newborns among rural populations in Rakai, Uganda. Maternal self-medication with nevirapine tablets at onset of labor followed by maternal provision of nevirapine syrup to most newborns within 24 hours and to all by 72 hours after birth resulted in a low rate of MTCT (7.5 percent), which is comparable to rates observed in clinical trials. In addition, the MTCT rate of 7.5 percent in the study population (compared with 19.4 percent before initiation of the nevirapine program), suggested that mothers could effectively provide nevirapine to themselves and to their newborns and reduce MTCT by approximately 60 percent compared with historic levels. Ninety-two percent of the women in the study population accepted voluntary counseling and testing for HIV, 100 percent of the women identified as HIV positive in the study accepted nevirapine, and 87 percent followed up postpartum. The methodology of allowing HIV-positive mothers living in rural Rakai to administer nevirapine to their newborns provided a "proof of concept" that is applicable to other rural regions.

Reversing a Risk Factor for Nevirapine Associated HIV-1 Resistance

Although mothers could effectively provide nevirapine to themselves and their newborns and achieve low rates of perinatal HIV infection in Rakai, Uganda, the results of a follow-on study in Botswana, released almost one year later, showed that single doses of nevirapine during labor often leads to viral nevirapine resistance in mothers and infants. This results in poor anti-HIV therapy outcomes with treatment regimens of drug combinations that contain nevirapine. A collaborative study by researchers in Boston, MA at the Harvard School of Public Health, the Beth Israel Deaconess Medical Center, the Brigham and Women's Hospital, and at the Botswana Ministry of Health showed that a woman's response to HIV treatment with nevirapine-containing drug combinations is improved if at least six months have passed after the receipt of nevirapine as a single dose during labor to prevent passing HIV to her child. To conduct the second study, the researchers followed 218 women in Botswana who volunteered for a prior study to test the effectiveness of nevirapine in combination with AZT in preventing the spread of HIV from mothers to their children. All women received a course of AZT from the 34th week of pregnancy to delivery. After randomization, one cohort received a single dose of nevirapine given at the beginning of labor and the other received a placebo. Infants received a single does of nevirapine or placebo at 48 to 72 hours after birth. Of the women participating in the study, 60 required anti-

retroviral therapy (ART) within six months after receiving either single dose nevirapine or placebo during labor. Of the women in the nevirapine group, 41.7 percent still had detectable HIV levels in the blood after receiving six months of ART, indicating that ART was not effective. In the placebo group, none of the women receiving the nevirapine placebo had detectable HIV in the blood after six months of ART. The study authors concluded that nevirapine-based ART is an option for women who require therapy six months or more after receiving a single dose nevirapine-preventative regimen. Women who receive single dose nevirapine to prevent MTCT and who require ART before six months have passed should receive ART that does not include nevirapine.

HIV in Women

Today, women account for nearly half of all people living with HIV worldwide. Over the past two years, the number of HIV-positive women and girls has increased in every region of the world, with rates rising most rapidly in Eastern Europe, Asia, and Latin America. In sub-Saharan Africa, 76 percent of the young people (aged 15 to 24 years) living with HIV are females (http://www.unfpa.org/hiv/women.htm). Accordingly, it is important to identify and address those factors that facilitate HIV transmission. Several FIC-supported studies that address HIV transmission and HIV progression in women and their outcomes are highlighted below.

Plasma Selenium Concentrations May Increase HIV Transmission

Selenium supplementation has significant health benefits in HIV-positive people, including stabilized viral loads and moderate gains in T helper (CD4) cells, but a recent study suggests that high levels of plasma selenium results in an increased risk for genital tract viral shedding in pregnant women. Shedding of HIV-1 in the female genital tract and increased levels of interleukin-1ß (IL-1ß), a marker of genital tract inflammation, are mediators of heterosexual HIV transmission and of mother-to-child HIV transmission. Researchers at the Harvard School of Public Health, the University College of Health Sciences in Dar es Salaam, Tanzania, and the Brigham and Women's Hospital at Harvard Medical School carried out an observational study during which selenium levels and genital tract viral shedding were examined in a group of 340 HIV-infected pregnant females at 27 weeks of gestation. During the antenatal and postnatal periods the randomized study participants received either: (1) ß-carotene/vitamin A, (2) multivitamins including ß-carotene/Vitamin A, (3) multivitamins without B-carotene/vitamin A, or (4) placebo. The study was nested within a randomized trial that examined the effect of vitamin supplements on maternal and child health outcomes. The researchers found that plasma selenium concentrations greater than 114 µg/l were associated with an increased risk of HIV-1 shedding and that this adverse effect was limited to women who received supplements that contained ß-carotene and vitamin A. There was no association between plasma selenium levels and IL-1ß concentrations. The study suggests that selenium may act synergistically with vitamin A and ß-carotene in ways that promote viral shedding. Vitamin A has been shown to increase HIV replication in cell cultures. By promoting the differentiation of myeloid and lymphoid cells, vitamin A could potentially increase the number of cells in the genital tract that can be infected by the HIV virus. In addition, ß-carotene has antioxidant properties under some conditions and under others it has pro-oxidant effects. The exact mechanism(s) by which selenium interacts with vitamin A and ß-carotene is unknown and remains to be elucidated in studies that focus on clarifying the role of selenium status as it relates to HIV-1 transmission.

Vaginal Washing as a Risk Factor for Increased HIV-1 Transmission

In populations where vaginal washing is common, the practice may be an important factor in promoting the spread of HIV-1. Researchers at the University of Washington at Seattle and the University of Nairobi in Kenya collected data on the vaginal washing practices of a cohort of about 1,496 women over a 10-year period and analyzed vaginal washing as a time-dependent variable. Among the 1,270 women who returned for followup, HIV-1 seroconversion occurred in 222. Compared with women who did not perform vaginal washing, those who used water experienced

nearly a three-fold increased risk of HIV-seroconversion, while those who used soap had approximately a four-fold increased risk. A causal association between vaginal washing and HIV-1 acquisition seems biologically plausible. Vaginal cleansing using water, soap, or other substances, including detergents, antiseptics and herbs, is a highly prevalent practice in Kenya and could: (1) disrupt the genital mucosa or cause inflammation; (2) disrupt normal vaginal flora, decreasing colonization with Lactobacillus species; or (3) cause an increased susceptibility to genital tract infections. However, analyses controlling for STDs, bacterial vaginosis, and candidiasis suggest that the increase in HIV-1 susceptibility may be at least partially independent of genital tract infections. In order to develop culturally appropriate HIV intervention strategies, more studies are needed to increase understanding of the norms and beliefs surrounding the use of intra-vaginal cleansing practices in diverse populations.

Hormonal Influences on HIV Disease

A number of studies, some cross sectional and others prospective, have found conflicting results on the impact of hormonal contraceptives on the acquisition and/or progression of HIV disease. A key difference among these studies has been the study population—some involved women within the general population and others involved women with high-risk behaviors. Researchers at the University of Washington in Seattle, the University of Nairobi in Kenya, and at the Coast Provincial General Hospital in Mombasa, Kenya conducted a large study of more than 1,500 women with high-risk behaviors to examine the association between hormonal contraception and HIV-1 seroconversion. The aim of the study was to describe the linkage between HIV-1 seroconversion, virological, and clinical characteristics of early HIV-1 infection, and the natural history of HIV disease among African women who used hormonal contraceptives. The study was initiated in 1993. Of the 1,500 participants taking hormonal contraceptives, 248 seroconverted for an overall incidence of 8.5 per 100 woman-years. In this study, the term "woman years" was adapted to indicate the number of women who seroconverted for each 100 participants in the study. ("Woman-years" is usually a term that describes the effectiveness of contraceptives over a one-year period.) At monthly followup visits, sexual behavior and contraceptive use were recorded, and laboratory screening for HIV-1 and STP was performed. The results suggested that hormone use among high-risk women predisposes them to the acquisition of a diverse virus population, which in turn leads to higher levels of viral replication and more rapid HIV-1 disease progression. An analysis of the genetic characteristics of the viruses infecting a subgroup of the women showed that all viral populations derived from single sexual encounters rather than superinfection from multiple partners. Although the exact mechanism is unknown, several mechanisms have been proposed for how female hormones may affect HIV-1 infection, including physiological effects on the integrity of the vaginal epithelium, an effect on the cell-surface levels of CCR5, which is a key molecule for HIV-1 entry, or a direct effect on virus expression. Additional studies in both developed and developing country settings should be conducted to assess the interaction between hormonal contraception and HIV-1 within the context of antiretroviral therapy and within the context of general and high-risk study populations.

Co-infection with Human Papillomavirus (HPV) May Speed the Progression of HIV Infection

Co-infection by human papillomavirus (HPV), which plays a role in the etiology of cervical cancer, may influence the progression of HIV disease by at least two potential mechanisms: by recruiting potential target cells in the immune system, such as CD4 cells and macrophages, and by inducing the local production of modulators of inflammation, such as interleukin (IL)-6, interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α). Researchers at Brazil's Oswaldo Cruz Foundation in Rio de Janero, the University Hospitals of Columbus in Ohio, and the David Geffen School of Medicine at University of California at Los Angeles characterized the immune system profile in the uterine cervix of 17 HPV-infected women compared with 17 women co-infected with HPV and HIV-1. The researchers found that HPV infection was associated with a marked increase in immune cells expressing IL-6, IFN-,

and TNF-; and co-infection by HPV and HIV-1 was associated with a decreased expression of the three cytokines. While the study could not differentiate which infection came first in women co-infected with HPV and HIV, it was clear that HPV infection increased the number of microphages—the primary target for HIV-1—in the cervix, and the distribution of HIV in cervical tissue followed the distribution of macrophage traffic to regional lymph tissues. Overall, the work describes a marked increase in T cell and microphage activation in HPV infection of the cervix that may facilitate HIV infection both in an increase in the target for HIV-1 infection and in the initial viral load presented to regional lymph nodes. Additional studies are needed.

Depressive Symptoms Increase Risk of HIV Disease Progression and Mortality among Women in Tanzania

A growing body of evidence linking psychosocial factors to immune suppression suggests that depression or stress may accelerate HIV disease progression, either through immunologic parameters (i.e., reductions in killer lymphocyte cells), impaired neuroendocrine function (i.e., altering serotonin and norepinephrine function), or behavioral mechanisms (i.e., non-adherence to medical recommendations). Researchers at the Harvard School of Public Health, the Muhimbili University College of Health Sciences in Dar es Salaam, Tanzania, and the Harvard Medical School are conducting a randomized controlled trial on the effect of vitamin supplementation on pregnancy outcomes, vertical HIV transmission, and HIV disease progression.

The investigators also followed a group of approximately 1,000 women for six to eight years, examining the effect of depression on HIV progression. Depression was determined using a simple eight-item screening tool. The researchers found a high prevalence of depressive symptoms (43 percent) among predominantly asymptomatic HIV-infected pregnant women approximately two months after learning about their HIV status; and more than half (57 percent) reported depression at least once during pregnancy or during the study followup period, defined as more than 12 months postpartum. These prevalence estimates of depression among Tanzanian women are consistent with a cross-sectional assessment of depression among HIV-infected men and women in Uganda and are similar to those in a U.S. cohort of HIV-infected women. After adjusting for clinical or immunologic predictors and sociodemographic correlates of disease progression, depressive symptoms among HIV-infected women were associated with a significant increased risk of clinical disease progression to World Health Organization (WHO) stages III (i.e., symptomatic HIV infection) and IV (i.e., progression from HIV to AIDS). Depression also was predictive of a greater than two-fold increased risk of death. Effective interventions for managing depressive symptoms are needed, but there is concern that apprehension about confidentiality, fear of HIV serostatus disclosure, and stigmatization may inhibit full participation in counseling or peer support interventions. Accordingly, barriers to participation in psychological support mechanisms need to be investigated and addressed through operational research.

Rapid Scale-up of Antiretroviral Therapy (ART) in Resource Limited Settings

Rapid Scale-up of ART at Primary Care Sites in Zambia Using Non-physician Clinicians: Feasibility and Early Outcomes

The initiation of a pilot public sector ART program by the Zambian Ministry of Health (MOH) at two of the country's largest hospitals in 2002 quickly showed that the sheer magnitude of the nation's AIDS epidemic would outstrip the number of available physicians and the ability of the hospital system to cope. With funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis and Malaria, and other sources, the Zambian MOH initiated ART services in 2004 at four urban clinics, this time using mostly non-physician clinicians. Researchers at the Schools of Medicine and Public Health at the University of Alabama at Birmingham, the University Teaching Hospital at Lusaka, Zambia, the School of Public Health at University of North Carolina at Chapel Hill, and the Zambian MOH reported their experiences with the rapid scale-up of

ART treatment for more than 21,755 patients entering the program, of which 13,646 or 63 percent were female. Eligibility for treatment was determined according to government guidelines. Of the 21,755 HIV-infected adults who appeared for eligibility testing, 16,198 started treatment and contributed 207 days of followup analysis. Moreover, 5,557 non-qualifiers for ART contributed approximately 74 days to analysis. Approximately 18 months after the start of ART, 72 percent of the patients remained alive, 7 percent had died, 21 percent were categorized as late to followup, and less than 1 percent withdrew. Patients starting ART were older, less likely to be female, had lower mean BMI, and more likely to have severe anemia compared with patients not initiating treatment. The study outcomes in Zambia indicated that massive, rapid scale-up of AIDS treatment services is feasible in urban sub-Saharan Africa and that favorable clinical outcomes are possible in settings where nurses and clinical officers provide the majority of the care. The program's mortality rate of five deaths per 100 patients after the first 90 days was comparable with that observed in developed world settings. The success of the program was attributed to four factors: (1) key leadership and political advocacy by the Zambian government, (2) circumvention of the critical physician shortage with the use of clinical officers and nurses, (3) electronic patient tracking and outcomes monitoring system, and (4) huge financial resources made available by PEPFAR. The principal limitation of the analysis was the relatively high number of late and lost-to-followup patients. While a home followup visit was helpful for ascertaining death outcomes, it proved inefficient and relatively expensive for generating return patient visits. A major barrier to getting patients into care early is stigma. And despite successes, operational issues, such as patient overload, staff burnout, and clinical management issues (i.e., multiple regimen failure, long-term adverse effects, program attrition, and expanding access to remote regions) are still concerns.

Assessing the Use of Antivirals from a Public Health Perspective

Current WHO guidelines for initiating anti-retroviral treatment are based on markers of advanced disease, and the focus is on the potential risk versus benefit to individual patients. Researchers at the University of Washington in Seattle and the University of Nairobi in Nairobi, Kenya took a different approach and investigated the potential public health benefit of ART in a cross-sectional study. This study simultaneously evaluated markers of infectivity (i.e., genital HIV-1 shedding) and sexual risk behavior among a cohort of Kenyan women. The cohort was stratified according to WHO criteria for initiating ART, utilizing both CD4 cell count (i.e., CD4 cell counts less than 200 cells/μL) and presence of symptoms. The results were consistent with previous studies that showed a stepwise increase in genital HIV-1 shedding with increasing levels of immunosupression and symptomatic disease. But increased immunosupression was associated with fewer sexual encounters and less risky sexual behavior. Although the findings do not prove that HIV-1 progression resulted in decreased sexual activity or that sexual frequency would increase with immune recovery due to ART, the study highlights questions for further study as anti-retroviral programs are scaled up. Can anti-retrovirals prove to be an important tool for decreasing the sexually transmitted epidemic of HIV-1 infection in resource-limited settings? While additional work must be done to increase understanding of the risk of HIV-1 transmission among individuals who would qualify for ART under current WHO guidelines and those who do not, the current study suggests that women with early or intermediate stages of HIV-1 infection may be an important target population for interventions, including anti-retrovirals, that reduce the risk of sexual transmission.

New Diagnostics for Use in Resource Limited Settings

Low-cost Detection of Iron Deficiency

Given the prevalence of iron deficiency anemia in the poorest parts of the world and the costs of screening for other causes of anemia, many pregnant women with anemia are treated as iron deficient based on low levels of hemoglobin and the median red cell blood volume without screening for other causes of microcytic anemia, a blood disorder characterized

by abnormally small red blood cells. This practice exposes patients with microcytic anemia, which is due to causes other than iron deficiency, to known adverse effects of iron treatment. Researchers at Pennsylvania Hospital and the School of Medicine at the University of Pennsylvania conducted a study to elucidate if anemia in pregnancy caused by iron deficiency could be predicted by simple measures that could easily be obtained on a complete blood count. The goal was to maximize specificity while maintaining high sensitivity to discriminate anemia caused by iron deficiency in pregnant patients from the conditions with similar characteristics. Red blood cell indices, such as hemoglobin, number of red blood cells, red cell distribution width, mean corpuscular volume, and other measures, were obtained in a cohort of 141 women that included patients in all three trimesters of pregnancy. Forty-seven pregnant women were considered iron deficient based on ferritin levels (i.e., less than 10 ng/mL), which is the gold standard for diagnosing iron deficiency anemia. Using the data, the researchers created a simple scoring system involving three indices: hemoglobin (Hb), red cell distribution width (RDW), and gestational age of less than 20 weeks to predict iron deficiency anemia. Upon assigning one point to each of the variables, a value of greater than or equal to two was defined as the predictor of iron-deficiency anemia with the highest specificity (88.3 percent) while maintaining good sensitivity (44.7 percent). The results were consistent with previous studies that found RDW to be a useful tool to differentiate among different causes of microcytic anemia. Although the results must be validated in areas with more diverse racial and ethnic origins (the study included 132 African Americans, five Asians, one white female, and three from other racial groups), the results provide evidence that iron-deficiency anemia can be predicted in pregnancy using lower cost tests. The development of a scoring system to diagnose iron deficiency in pregnant women with anemia is a very useful tool, not only in the poorest latitudes of the world where resources are limited, but such a practice also promotes the better utilization of resources in developed countries with a high prevalence of diverse causes of microcytic anemia in pregnancy.

Exploring Meconium to Determine Intrauterine Exposure to Environmental Neurotoxicants

Exposure to neurotoxicants during critical periods of brain development can produce permanent cerebral dysfunction from infancy, or the adverse effects can be delayed until adulthood. Researchers at the Institute of Chemical and Environmental Research in Barcelona, Spain, the University Children's Hospital in Murcia, Spain, and the Mount Sinai Medical Center proposed that the newborn's meconium or first stools could be used to explore a low-cost method for assessing exposure to neurotoxicants during development. Once toxic substances or metabolites reach the meconium, they remain "fossilized" and may provide a measure of the scope and timing of maternal exposure to environmental neurotoxicants. Meconium consists of a series of layers of epithelial cells, bile acids/salts, and products derived from swallowing amniotic liquid, etc. This forms in the intestines during gestation and begins to accumulate from the 12th or 13th week of pregnancy. The researchers conducted an exploratory study to determine whether neurotoxicants, specifically organochlorine compounds (OCs), could be detected in serially collected meconium from 10 newborn infants. Previous studies proposed that meconium taken between 0 and 10 hours of life reflects the first 20 weeks of exposure, between 11 and 20 hours corresponds to 30 weeks of exposure, and between 21 and 36 hours corresponds to a gestational age greater than 30 weeks. The results of the exploratory study showed that organochlorine compounds were quantifiable in both the cord blood and meconium and that the concentration of OCs in cord blood is highly correlated with the concentrations in the meconium. The results also showed an increase in the concentrations of OCs from the first stool of the newborn to the last one. The increase in fetal-placental blood circulation system could explain the increase in the concentration of metabolites throughout pregnancy. While the analysis and interpretation of results obtained using meconium is a complex process and additional studies are needed, the exploratory results are encouraging. Due to its physiological characteristics, meconium could be a new economic and sensitive tool for studying the exposure

timing to chemical neurotoxicants, and knowledge of exposure timing could help to minimize and prevent short- and long-term adverse effects to newborns.

Investigating Adverse Environmental Influences

Dietary and Genetic Determinants of Homocysteine Levels among Mexican Women of Reproductive Age

Elevated plasma homocysteine, especially at a level of 15 micromoles/liter (μmol/l) or higher, is considered a risk factor for adverse reproductive outcomes, including preeclampsia, preterm birth, and very low birth weight. Elevated plasma homocysteine is associated with a variant of methylene tetrahydrofolate reductase (MTHFR), a key enzyme in the pathway that leads to the conversion of homocysteine to the amino acid, methionine. The presence of the enzyme variant, in combination with a decreased availability of folate and vitamin B12 in the diet, leads to increased levels of circulating homocysteine, which can be toxic to the developing embryo in pregnancy. Researchers at the National Institute of Public Health in Morelos, Mexico, the Mount Sinai School of Medicine, and the Baylor University Medical Center investigated the independent and joint effects of dietary folate and B12 and MTHFR polymorphisms on serum levels of homocysteine and folate in women of reproductive age from the state of Morelos, Mexico. The prevalence of the MTHFR 677T variant in the Mexican study population (52.5 percent) is one of the highest in the world, and 26 percent of the women were homozygous for the 677TT genotype. The study showed that the consumption of vitamin B12 was inadequate among 15.4 percent of the study population, and the consumption of folic acid was inadequate among 47.7 percent. Among women with the 677TT MTHFR variant, the decreased availability of vitamin B12 led to an accumulation of the embryotoxin, homocysteine, presumably due to the prevention of the conversion of homocysteine to methionine through a vitamin B12 dependent reaction. The study suggests that the supplementation with folic acid alone, both before and during pregnancy, should be considered only as a partial solution; combining folic acid supplementation with other B vitamins, particularly B12, is preferable. Folic acid supplementation alone is likely to mask a deficiency in vitamin B12 and hampers the possibility of correcting the levels of homocysteine.

Pregnancy Outcomes, Infant Mortality, and Arsenic in Drinking Water in West Bengal, India

South Asia, including Bengal, India and neighboring Bangladesh, are particularly affected by naturally occurring arsenic in well water; and exposures to concentrations of 100μg/liter exceed the recommended standard (10μg/liter) by the U.S. Environmental Protection Agency (EPA) and the WHO by 10-fold. Arsenic concentrations in drinking water above 50 μg/liter have been related to increased risks of spontaneous abortion, stillbirth, preterm delivery, and infant mortality. Researchers at the School of Public Health at the University of California at Berkeley, the Institute for Postgraduate Medical Education and Research in Kolkata, India, the California Department of Health Services, and the School of Public Health at the University of Washington conducted the first retrospective study of the relation of arsenic exposure during pregnancy to pregnancy outcomes and infant mortality among 202 married women in West Bengal, India. Arsenic concentrations were documented for all sources of water used by the study participants during the time period of their pregnancies. In earlier studies, the overall duration of exposure was considered without specifically taking into account exposure during their pregnancies. The average prenatal concentration of arsenic in drinking water was 101.7 μg/liter, with 18.2 percent of pregnant women being exposed to levels greater than or equal to 200 μg/liter. The data showed a sixfold increase in risk of stillbirth at high arsenic levels equal to or greater than 200 μg/liter after adjusting for socioeconomic variables and other potential confounders. Women with arsenic-related skin lesions had a 13 times higher risk of ever having a stillbirth than women without skin lesions. No association was found between spontaneous abortion or overall infant mortality and arsenic exposure during the first year of life and prenatal arsenic exposure. The potential linkage between

arsenic exposure and stillbirth needs to be confirmed. However, the existing evidence warrants preventive actions designed to reduce the exposure of childbearing-age women in regions with high levels of arsenic in water.

Initiatives

Request for Applications (RFAs)

- **International Tobacco and Health Research and Capacity Building Program (Tobacco)**
  This program supports trans-disciplinary research and capacity building projects that address the burden of tobacco consumption in low- and/or middle-income nations by: (1) pursuing observational, intervention, and policy research of local importance, and (2) building capacity in these regions in epidemiological and behavioral research, prevention, treatment, communications, and health services and policy research. An example of a project supported by the Tobacco program that focuses on international women health includes a study on exposure to environmental tobacco smoke.

Program Announcements (PAs)

- **AIDS International Training and Research Program (AITRP)**
  This program supports HIV/AIDS-related research 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 effort.
- **Brain Disorders in the Developing World: Research Across the Lifespan (BRAIN)**
  This program supports the development of collaborative research projects to study brain disorders relevant in low- and middle-income nations throughout life. Training and capacity building opportunities are also supported within the context of the proposed research. Some examples of research supported by the BRAIN program that focus on women's health include postpartum depression, psychiatric disorders/HIV interface in women, psychological trauma, and neurotoxins/neurotoxicants in the home.
- **Fogarty International Research Collaboration (FIRCA)**
  This program provides funds to foster international research partnerships between NIH-supported investigators and their collaborations in countries of the developing world. The FIRCA Program aims to benefit the research interests of both U.S. and developing country collaborators while increasing research capacity at the foreign site. All areas of biomedical and behavioral research supported by the NIH are supported, except research related to HIV, AIDS, or related illnesses. The program publishes two companion program announcements—International Research Collaboration: Behavioral and Social Sciences and International Research Collaboration: Basic Biomedical. Some examples of research supported by the FIRCA program that focus on international women's health include obesity in women, cervical cancer, breast cancer, and smoking cessation in women.
- **Framework Programs for Global Health (FRAMEWORK)**
  This program aims to build global health research capacity in the U.S. and in low- and middle-income countries by supporting the development of innovative, multidisciplinary global health programs. Through Framework programs, institutions develop curricula for undergraduate, graduate, and professional school students and create administrative frameworks to build multiple schools (such as engineering, business, arts and sciences, law, communications, public health, medicine, environmental studies, and others) on the topic of global health.
- **Global Infectious Disease Research Training Program Award (GID)**
  This program addresses research training needs related to infectious diseases that are predominantly endemic in or impact upon people living in developing countries. The

ultimate goal is to build a critical mass of researchers and support staff to conduct independent infectious disease research in developing country institutions.

- **Global Research Initiative Program, Basic/Biomedical Sciences and Social Science (GRIP)**
  This program promotes productive re-entry of NIH-trained developing country investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, to stimulate research on a wide variety of high priority health-related issues in such countries, and to advance the NIH efforts to address health issues of global import. Examples of research supported by the GRIP program that focus on international women's health include family structure/dynamics, preterm birth, widow inheritance and HIV infections, ovarian and breast cancer, female-controlled HIV prevention, iron deficiency anemia, and Balkan endemic nephropathy in women.
- **International Training and Research in Environmental and Occupational Health (ITREOH)**
  This program provides training for health scientists, clinicians, epidemiologists, toxicologists, engineers, industrial hygienists, chemists, and allied health workers in developing countries and emerging democracies in both general environmental and occupational health research. Examples of projects supported by ITREOH that focus on international women health include pesticide exposure and reproductive function, methylene tetrahydrofolate reductase variants in women, timing of perinatal exposures, and breast cancer.

Conferences and Workshops

- **International Women Scientists Featured in International Women's Day Celebration**
  International Women's Day, celebrated on March 8 each year, is a major day of global celebration for the economic, polices, and social achievements of women. At the NIH, we celebrate the important achievements in science of women worldwide and recognize the impact their achievements have had on our quality of life. In March 2005, investigators from different countries and supported by different NIH ICs presented their work and participated in a discussion titled *International Women Scientists at NIH: Their Research and Career Paths*. These investigators included Dr. Grace Yeh of Taiwan (NCI), Dr. Maria Morasso of Venezuela (NIAMS), and Dr. Linda Peters of New Zealand (NIDCD). The NIH Director, Dr. Elias Zerhouni, joined the FIC Acting Director, Dr. Hrynkow, and the ORWH Director, Dr. Vivian W. Pinn, in providing comments about the import of the event.
- **The Women's Global Health Scholars Program**
  Recognizing the continuing gender gap in academia, especially in scientific disciplines, the Women's Global Health Scholars Program was designed to equip women health scientists from around the world with the tools, skills, and networks needed to advance their careers and assume leadership positions. Twenty-eight women were selected from a competitive pool of nominees to participate in the one-year program. Hailing from Africa (Kenya, Malawi, Tanzania, South Africa, Uganda, Zimbabwe, Botswana), Asia (China, India, Vietnam), Eastern Europe (Turkey, Georgia), and Latin America (Brazil, Argentina, Peru), the scholars represented a range of disciplines from bioinformatics to social epidemiology. They are at different stages in their careers, from doctoral students to junior faculty. The program is composed of two one-week courses held at University of California, San Francisco, with monthly virtual seminars and meetings held in between. The first class was held September 17-23, 2006. During the live and virtual sessions, scholars work together to identify the biases, hierarchies, and structures that women confront in academia and devise strategies to overcome them to ensure their continued professional development. The program is sponsored by the FIC and hosted by Dr. Nancy Padian, the Director of the Women's Global Health Imperative at the University of California, San Francisco.

- **Virtual Program for Career Development and Capacity Building for Latin American and Caribbean Junior Women Scientists** This program made use of virtual workshops, interactive electronic fora, and videoconferences to encourage the empowerment and promotion of women scientists in various institutional contexts. The aims were to provide tools to promote career development of women in Latin America and the Caribbean as independent scientists, to encourage women scientists to take transformative leadership roles in their professional fields, and to promote equal opportunities for women and men in scientific institutions. The FIC and the United Nations Educational, Scientific, and Cultural Organization (UNESCO) cosponsored this virtual career development program with the Facultad Latinoamericana de Ciencias Sociales in Argentina. The program utilized innovative information and communication technologies, such as *Eluminate*, a Web conferencing and e-learning software. It used the technological and pedagogical expertise of the UNESCO Chair in producing and conducting the e-learning program on gender and science issues in Latin America. The participants included 15 Latin American women scientists from Argentina, Brazil, Colombia, Chile, and Mexico, as well as Fogarty GRIP grantees, NIH alumnae, and a FIRCA grantee.

Health Disparities among Special Populations of Women

A research study completed during FY 2005 and 2006 pertained to health disparities among special populations of women. It was titled Mother-to-Child HIV Transmission in Rural Ugandan Populations. The goal was to develop a new proof of concept for increasing access to nevirapine for HIV-positive mothers and their newborns living in rural areas. A single dose of nevirapine, administered at the onset of labor and provided to newborns within the first 24 to 48 hours of live protects the newborn against mother-to-child HIV transmission in resource poor countries. The study showed that rural Ugandan HIV-positive pregnant mothers could successfully administer the single dose of nevirapine to themselves as well as to their newborns, reducing the mother-to-child rate of HIV transmission to 7.5 percent in the study population, as compared with 19.4 percent prior to the initiation of the nevirapine program. The methodology of allowing HIV-positive mothers living in rural Rakai to administer nevirapine to their newborns provided a "proof of concept" that is applicable to other rural regions. The study is described in more detail in the previous Accomplishments section.

NATIONAL CANCER INSTITUTE

This report describes many of the activities and accomplishments of the National Cancer Institute (NCI) research programs in FY 2005 and 2006 addressing cancers that are specific to women, primarily affecting women, or with high incidence or mortality rates among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as AIDS and AIDS associated malignancies.

Cancer continues to take a devastating toll on American women. In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in cancer affecting women. Incidence rates for cancer of all sites, sexes, and populations combined have been stable from 1992 through 2003 after increases that started in 1975. The pattern of aggregate incidence was similar for men. Incidence rates for cancer overall for women were stable from 1975 through 1979 and then increased from 1979 through 2003. However, breast cancer incidence rates for women had a statistically non-significant decrease from 2001 through 2003. Overall, there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003, including a 14 percent decrease in 50- to 60-year-old women who had been diagnosed with estrogen receptor (ER) positive breast cancer. The decrease in this group may be due to the recent decline in use of hormone therapy (HT) by postmenopausal women. The overall cancer death rates for all sites, sexes, and race/ethnic populations decreased from 1994 through 2003, with the

annual rate of decline in men being twice as large as the annual decline for women. Mortality has decreased for all cancers combined in the general population and for 10 of the top 15 cancers in women. Lung cancer death rates among women continue to increase, although at a slower annual rate in more recent years. Survival rates for cancer patients diagnosed in the years 1975 to 1979, compared with those diagnosed from 1996 to 2002, show improvement overall, although the amount of improvement is slightly less 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. The NCI's Office of Women's Health, located within the NCI 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 both intramurally at the NCI and extramurally through research grants, a number of specific programs and activities focus on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium (BCSC) and the International Breast Screening Network in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group (GOG) and the Clinical Trials Cooperative Group in the Division of Cancer Treatment and Diagnosis, the intramural Breast and Gynecologic Malignancies Faculty, and the trans-NCI Human Papillomavirus (HPV) Working Group.

In addition to research with a primary focus on women's health, the NCI supports broad-based research programs that apply to all types of cancer in women, men, and children. 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 reduce the burden of cancer in all populations. The NCI strategic plan (http://strategicplan.nci.nih.gov/), which was released in 2006, details eight strategic objectives in two broad areas: (1) To Preempt Cancer at Every Opportunity and (2) To Ensure the Best Outcomes for All. The NCI supports research programs to expedite progress toward the following objectives.

Research in the first area, To Preempt Cancer at Every Opportunity, focuses on four strategic objectives. To address the first objective, Understanding the Causes and Mechanisms of Cancer, research is being conducted to discover the causes and mechanisms of cancer. This is essential to develop and apply treatments or interventions to keep cancers from starting or progressing. The NCI research portfolio supports basic, clinical, and population research to better understand how genetic, epigenetic, environmental, behavioral, and sociocultural factors relate to cancer. The second objective, Accelerating Progress in Cancer Prevention, is addressed through the NCI's portfolio supporting research to identify medical and behavioral approaches to cancer prevention that can be applied in public health settings. Prevention research focuses on risk assessment, systems biology, behavior modifications, environmental and policy influences, medical and nutritional approaches, and training and education for research and health professionals. Ongoing research related to the third objective, Improving Early Detection and Diagnosis, supports the development and dissemination of interventions to detect and diagnose early-stage malignancy with the goal of improving the odds for successful treatment and reduction in mortality. And research related to the fourth objective, Developing Effective and Efficient Treatments, focuses on discovering, developing, and evaluating more efficient and effective treatment strategies with little or no harm to healthy tissue.

Research related to the second area, To Ensure the Best Outcomes for All, encompasses four additional strategic objectives. To address the first objective, Understanding the Factors that Influence Cancer Outcomes, the NCI is intensifying its efforts to define, foster, and support studies to improve the understanding of factors affecting the outcomes of cancer and the impact of cancer care. Research focuses on understanding and measuring environmental, behavioral, sociocultural, and economic influences that affect the quality of cancer care, survivorship, and health disparities. The second objective, Improving the Quality of Cancer Care, high-quality cancer care requires delivering the full range of evidence-based

interventions that are safe, patient-centered, effective, timely, efficient, and equitable. Such care must be provided with technical competence and cultural sensitivity and must foster patient choice based on informed decision making. NCI research supports the development and dissemination of quality improvement interventions and methods to measure their success in improving health-related outcomes across the cancer continuum. To address the third objective, Improving the Quality of Life for Cancer Patients, Survivors, and Their Families, the NCI supports research on the development and dissemination of interventions to reduce the adverse effects of cancer diagnosis and treatment and to improve health-related outcomes for cancer patients, survivors, and their families/caregivers. Finally, the fourth objective, Overcoming Cancer Health Disparities, focuses on the best opportunities to lessen the burden of cancer for all. The NCI's investments are speeding the development and use of interventions to combat disparities across the cancer control continuum and among all underserved populations. The NCI supports research to identify factors contributing to disparities, to develop culturally appropriate approaches, and to disseminate interventions to overcome those disparities across the cancer control continuum from disease prevention to end-of-life care.

The NCI staff participate in multiple, diverse scientific partnerships and collaborative activities with other federal and nonfederal scientists that benefit women as well as men and children. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, the NCI staff take advantage of opportunities to accelerate the pace of discovery and facilitate the translation of research knowledge into clinical application. The following are examples of such activities.

- **The NCI Community Cancer Centers Program (NCCCP)**
  The NCI is launching the NCCCP in early 2007 as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multispecialty care to a much larger population of patients. The NCCCP complements other NCI initiatives to draw more patients into clinical trials in community-based settings; reduce health care disparities; prepare sites for standardizing the collection and storage of biological specimens for cancer research; link sites to national databases supporting basic, clinical, and population-based cancer research; and implement electronic medical records. Pilot sites will also share best practices and refine the overall concept as a prelude to launching a national network of research-driven cancer care at the community level.
- **Centers for Transdisciplinary Research on Energetics and Cancer (TREC)**
  The TREC centers have been developed to foster collaboration among transdisciplinary teams of scientists to accelerate progress to reduce cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. This program is part of the NCI's larger energy balance research focus, complementing the trans-NIH Obesity Task Force.
- **Cancer Intervention and Surveillance Modeling Network (CISNET)**
  The CISNET is a consortium of NCI-sponsored teams that use biostatistical modeling to improve understanding of cancer control interventions in prevention, screening, and treatment. The teams use data from randomized controlled trials, meta-analyses, observational studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions. Currently CISNET has teams focusing on breast, prostate, colorectal, and lung cancers.
- **Nanotechnology Alliance for Cancer**
  This alliance has begun harnessing nanotechnologies for cancer diagnostics, targeted imaging, and drug delivery. Multifunctional, targeted devices capable of bypassing biological barriers will enhance our ability to treat cancer effectively and efficiently by delivering therapeutic agents directly to cancer cells.
- **The caBIG™ (cancer Biomedical Informatics Grid™)**
  This initiative was launched to make information easier to share by connecting scientists and practitioners through a shareable and interoperable infrastructure that has

standard rules and a common language. caBIG™ will build or adapt tools for collecting, analyzing, integrating, and disseminating information associated with cancer research and care.

- **The Cancer Genome Atlas (TCGA)** The TCGA is a pilot project to assess the feasibility of a full-scale effort to systematically identify all genetic changes involved in human cancer. Investigators will study lung, brain (glioblastoma), and ovarian tumors. All data will be publicly available to researchers worldwide through caBIG™.

The NCI educates cancer patients, health and research professionals, and the public about women's health and cancer research in a variety of formats. Information is provided to the public, the cancer community, and journalists through the NCI Web site at http://www.cancer.gov. The NCI's Research on Cancers in Women Web page provides highlights of NCI-supported research to understand, prevent, diagnose, and treat cancers in women at http://women.cancer.gov. Cancer information is also provided through staffed NCI exhibits at key conferences, meetings, and events. The NCI Cancer Information Service (CIS) shares information about cancer prevention, risk factors, symptoms, diagnosis, treatment, research, and smoking cessation. CIS information specialists provide the latest, most accurate information about cancer by telephone (1-800-4-CANCER) and on the Internet through LiveHelp instant messaging service on NCI's Web site (http://cancer.gov). CIS also provides printed and electronic NCI publications through the NCI Pubs Locator available online at http://cissecure.nci.nih.gov/ncipubs/ or by calling 1-800-4-CANCER. Through its Partnership Program, 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.

Additional information on the NCI's research activities and accomplishments related to specific cancers that are found across the cancer continuum are described below.

Accomplishments

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 2007, an estimated 178,480 women are expected to be diagnosed with invasive breast cancer and 62,030 with in situ breast cancer. And an estimated 40,460 women will have died of the disease. More than 2.3 million women in the U.S. 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. Following long-term increases, breast cancer incidence rates for women decreased from 2001 through 2003, although this decrease was not statistically significant. Overall, there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003. There was a 14 percent decrease in incidence rates among 50- to 69-year-old women diagnosed with ER-positive breast cancer, which may have been due to the recent decline in use of HT by postmenopausal women. Death rates from breast cancer for all women began decreasing in the early 1990s, although the differential in mortality among racial/ethnic populations is widening. Although breast cancer survival rates have improved by about 14 percent since the mid 1970s, this progress is not impacting all populations equally. Even when controlling for age and stage of disease at diagnosis, breast cancer mortality rates vary greatly among racial/ethnic populations. The highest rates are seen in black women, followed by non-Hispanic white and Hispanic women. Rates are lowest in Asian Pacific Islander (API) and American Indians/Alaskan Native women.

An important component of the breast cancer portfolio is the Breast Cancer Specialized Programs of Research Excellence (SPOREs). Ten breast cancer SPORES conduct collaborative, multidisciplinary research to develop novel agents and technologies for breast cancer treatment and prevention and to

identify biomarkers for diagnosis, prognosis, screening, prevention, and targeted treatments. For example, SPORE researchers have shown that three tests, now in clinical testing, using gene expression patterns to predict breast cancer outcomes appear to be more predictive than traditional pathological data, such as tumor size and grade. Additional information on the SPORES can be found at http://spores.nci.nih.gov/breast/breast.html.

Biology and Genetics

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. For example, research suggests that breast cancers arise from a population of stem cells that are present in the normal mammary gland. Researchers are studying these breast stem cells to determine what events may initiate the tumorigenic process. Researchers also have developed comprehensive methods using ductal lavage and ductal endoscopy with endoscopic sampling to evaluate high-risk breast duct and ductal epithelium.

The NCI has initiated the unique Trans-NCI Breast Premalignancy Program using the proceeds of special-issue U.S. postal stamps mandated by the Stamp Out Breast Cancer Act. This comprehensive program encompasses prevention, etiology, biology, diagnosis, and molecular epidemiology research. Researchers are investigating the molecular epidemiology and biology of mammographic density, the biology of breast premalignancy and tumor stem cells, decisionmaking approaches to chemotherapy, strategies for early detection, and nano-imaging technologies.

In FY 2005 and 2006, researchers from the NCI Mouse Models of Human Cancers Consortium (NCI-MMHCC) developed and used mouse models to better understand breast cancer development and progression. For example, researchers derived a series of mouse models that reproducibly represent the progression of breast cancer from ductal carcinoma in situ (DCIS) to invasive malignancy. These models show that the major molecular and genetic changes required for metastasis are already present at the earliest stages in breast cancer lesions that eventually metastasize. This research also shows that changes leading to cancer and its progression can be subtle and inconsistent. A transgenic model of preneoplastic progression of breast cancer has been used to show that inflammatory cells play a critical role in mediating proliferation of breast epithelial cells and neo-vascularization. Small animal imaging allows exploration of functional changes as breast cancer develops and metastasizes and investigation of the tumor micro-environment and its role in metastasis. The NCI-MMHCC collaborations with epidemiologists have facilitated the discovery of four new common polymorphic human susceptibility genes, which were identified in mice and then assessed in human breast cancers. More information on the consortium is available at http://emice.nci.nih.gov/.

About 30 percent of human breast cancers show overexpression of the protein HER2. These tumors are aggressive, with a high rate of relapse and poor prognosis. Previous research has found Herceptin® (trastuzumab) therapy, which targets HER2, to slow disease progression in about one-third of patients with HER2-positive breast cancer, although these patients eventually develop resistance to the drug. Preclinical research continues to inform efforts to improve treatment efficacy in patients with HER2-positive tumors. One study suggests that inhibition of HER2 binding to the protein alpha-6-beta-4 may help combat resistance to HER2-targeted therapy. Another study has implicated the mTOR pathway in HER2 positive tumors that also overexpress the protein AIB1. Investigators suggest that tumors positive for HER2 and AIB1 may be more effectively treated with an ER inhibitor, such as tamoxifen, in combination with an inhibitor of the mTOR pathway.

Studies Directed toward the Eradication of Brain Metastases of Breast Cancer is a multi-institutional consortium supported by the U.S. DoD Breast Cancer Research Program Center of Excellence and led by NCI scientists. Studies focus on the mechanistic underpinnings of brain metastases and provide preclinical data to advance compounds to clinical trials for this devastating complication of breast cancer.

The NCI Consortium of Cohorts addresses the need for large-scale collaborations for the study of gene-gene and gene-environment interactions in the etiology of cancer. The

Breast and Prostate Cancer Cohort Consortium includes 10 cohorts with pooled data from 6,160 patients with breast cancer. Researchers will analyze common variations in about 50 candidate genes involved in steroid hormone metabolism and insulin-like growth factor signaling pathways for association with cancer risk. Another cohort study, The Cancer Genetic Markers of Susceptibility Project, is conducting scans of the entire human genome to identify common inherited gene variants that increase the risk of breast cancer.

The Cooperative Breast Cancer Tissue Resource Database 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. This resource has recently begun to provide tissue microarrays to researchers studying molecular signatures of breast cancer. More information on this database is available online at http://www-cbctr.ims.nci.nih.gov/.

Risk Factors

NCI scientists have confirmed reports that approximately one in every 200 women in the U.S. carries a CHEK2 gene that almost doubles the risk of developing breast cancer compared with women without this mutation. Another study estimates that certain mutations in a gene, BRIP1, which is associated with Fanconi anemia, may double breast cancer risk. Mutations in CHEK2, BRIP1, and a third gene, ATM, appear to predispose a woman to cancer only in the presence of other genetic or environmental risk factors.

A study supported through the NCI Breast Cancer Family Registry suggests that DNA repair capacity may be a valuable *in vitro* biomarker to identify women at high-risk for breast cancer, especially in those with a history of familial breast cancer. Lymphoblastoid cells of breast cancer patients were less effective than cells from their healthy sisters in responding to an *in vitro* chemical mutagenic assault, especially in cells from women younger than 40. The relative risk of breast cancer was nearly three times greater between the groups with the most and the least DNA repair capabilities.

There is well-established evidence indicating an association between decreased breast cancer risk and early age at first-term birth, increasing parity, and long duration of lactation. Breast cancer risk is temporarily increased for several years following pregnancy. However, no association has been found between increased breast cancer risk and either spontaneous or induced abortions. Other reproductive factors associated with increased risk of developing breast cancer include early age of first menstrual period, late age of menopause, and use of menopausal hormone therapy.

The NCI-sponsored Women's Intervention Nutrition Study was the first large-scale study to examine the influence of dietary fat on breast cancer outcomes in postmenopausal women treated for early-stage breast cancer. After five years, women on the low-fat diet showed a significant reduction in cancer recurrence compared with the control group (9.8 percent vs. 12.4 percent). Women on the low-fat diet who had been previously treated for non-estrogen-dependent cancer, which is typically associated with a greater likelihood of recurrence, had a 42 percent reduced risk of recurrence compared with those on a standard diet.

The NCI sponsored a scientific workshop in March 2006 titled *Feasibility of a Physical Activity, Weight Control Trial to Prevent Breast Cancer*. Workshop participants reviewed evidence to debate the feasibility, utility, and design issues for a possible clinical trial and to identify research gaps and opportunities to advance the field. A scientific report and planning for next steps are in progress.

The NCI is sponsoring the Women's Healthy Eating and Living (WHEL) Study, a multisite, randomized, controlled trial of the effectiveness of a high-vegetable, low-fat diet on reducing additional breast cancer events and early death in women with early-stage invasive breast cancer. Follow up of the 3,088 study participants will continue through 2006, and reports of primary outcomes are expected in 2007.

NCI-supported research is helping to clarify the effects of various hormones on breast cancer risk. In 2002, the Women's Health Initiative (WHI) published results of the Estrogen-Plus-Progestin Study, which found an increase in breast cancer in women taking combined hormone therapy. According to a new analysis of NCI Surveillance, Epidemiology, and End Results (SEER) data, breast cancer incidence in the U.S. dropped

sharply by 7 percent between 2002 and 2003. A decline of 14 percent was found in women between ages 50 to 69 diagnosed with ER-positive breast cancer. Researchers suggest that this drop may be associated with the reduction in use of hormone therapy by postmenopausal women. Other research has revealed an 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 since the 1970s, DES exposure was associated with an increased breast cancer risk among women aged 40 and older. Researchers will continue surveillance on this cohort.

Preclinical researchers investigating 2-methoxyestradiol (2ME2) found a paradoxical effect of this hormone on cancer risk. Although 2ME2 significantly reduced tumor growth at late stages, the data suggest that altered tumor morphology and accelerated tumor growth may occur if the hormone is administered in a prevention setting for prolonged periods.

Although much of the research of the Long Island Breast Cancer Study Project (LIBCSP) is complete and no association was found between residential electromagnetic fields and increased risk for breast cancer, further analyses and a followup study are in progress. Current research is aimed at defining breast cancer risk associated with environmental and lifestyle factors, including studies of regional differences in breast cancer rates in the U.S.; prenatal-to-adult environmental exposures potentially leading to breast cancer; possible relationships between dichloro-diphenyl-trichloroethane (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. The NCI also co-funds four Breast Cancer and Environment Research Centers (BCERC) with the NIEHS to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer. More information on the BCERC can be found at http://www.bcerc.org/.

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. Additional information on this resource is available at http://epi.grants.cancer.gov/BCFR/index.html.

Prevention

The Study of Tamoxifen and Raloxifene (STAR) compared these two selective ER modulators (SERMs) for reducing the incidence of breast cancer in postmenopausal women at increased risk for this disease. One of the largest breast cancer prevention studies ever, STAR took place at more than 500 centers across the U.S., Canada, and Puerto Rico. Initial results, released in April 2006, show that raloxifene is as effective as tamoxifen in reducing the breast cancer risk of trial participants. Both drugs reduced the risk of developing invasive breast cancer by about 50 percent. In addition, women taking raloxifene had 36 percent fewer uterine cancers and 29 percent fewer blood clots over a period of about four years than the women who were taking tamoxifen. More information on the STAR is available at http://www.cancer.gov/star/.

Breast cancer clinical trials are ongoing to test for preventive properties of the isoflavone, genistein; the statin, Simvastin; the selective rexinoid compound, bexarotene; the non-steroidal anti-inflammatory drug (NSAID), sulindac; and grape seed proanthocyanidin extract. The NCI is also supporting investigator-initiated research to identify potential molecular targets for prevention of human ER-negative breast cancer.

Cancer Research Network (CRN) investigators have reported that, in patients with cancer in one breast, contralateral prophylactic mastectomy reduced the risk of death from breast cancer by 43 percent after an average of five years of followup. A related CRN study found that, among women at elevated risk for breast cancer, less than 1 percent of women who received prophylactic mastectomy subsequently developed breast cancer, compared with 4 percent of women who did not undergo the surgery. Furthermore, recent research shows that prophylactic mastectomy in women with BRCA1 or BRCA2 mutations reduces risk of breast cancer by about 90 percent. Further research on potential physi-

cal and psychological harms of prophylactic mastectomy is needed.

A recent study of 1,439 patients with breast cancer and 1,866 matched controls found that a previous history of oophorectomy was associated with a significant reduction in breast cancer risk of 56 percent for BRCA1 carriers and of 46 percent for BRCA2 carriers. The benefit was greatest in women who had an oophorectomy before age 40, and the protective effect was evident for 15 years postoophorectomy.

There is ongoing research on physical activity and breast cancer prevention. Researchers are investigating the preventative effects of physical activity in women at high risk for or with a history of breast cancer.

Early Detection, Diagnosis, and Prognosis

The NCI invests in research to improve the efficacy and use of mammography. The Breast Cancer Surveillance Consortium (BCSC) studies breast cancer screening practices and fosters collaborative research to improve the practice of community-based mammography screening. Recent BCSC research found that inclusion of breast density in the Gail Model, an interactive model to predict breast cancer risk, improved prediction accuracy for both pre- and postmenopausal women. Another BCSC study has reported that inadequate use of screening mammography may be an important reason why black women are more likely to be diagnosed with advanced stage breast cancer than women of other ethnic groups. More information on the BCSC is available online at http://breastscreening.cancer.gov/index.html.

In 2006, the NCI and the American Cancer Society (ACS) began an initiative for Assessing and Improving Radiologists' Mammography Interpretive Skills. This project will examine factors that influence accuracy in the interpretation of mammograms to improve training and skill maintenance of interpreting physicians. An initial study has established a baseline of performance by radiologists from several facilities across the U.S. Another study reported that the number of radiologists appropriately recommending a short-interval followup (usually six months) increased from 51 percent in 1996 to 76 percent in 2001.

The NCI-supported American College of Radiology Imaging Network (ACRIN) Digital Mammography Imaging Screening Trial (DMIST) compared the efficacy of digital mammography and film-based mammography. Investigators reported that women with dense breasts, who are pre- or peri-menopausal or who are younger than age 50 would benefit from having a digital rather than a film mammogram. Analyses of reader variability and cost-benefit are in progress. More information about DMIST is available at http://cancer.gov/dmist.

A group of investigators used SEER data to identify any geographic association between the level of use of breast cancer screening and breast cancer mortality. Analyses suggested a moderate effect of mammography use on decreasing breast cancer mortality in the U.S., which support the conclusions of randomized mammographic screening trials.

The NCI is funding research on a variety of other technologies for breast imaging, including magnetic resonance imaging (MRI), ultrasound, magnetic resonance spectroscopy, computer-aided diagnosis, elastography, 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. For example, the Screening Breast Ultrasound in High-Risk Women Study is designed to assess the effectiveness of whole breast bilateral screening sonography combined with mammography as compared with mammography alone for the detection of breast cancer in women with dense breasts. Results are expected in early 2007 from a clinical trial to assess the performance and usefulness of high resolution MRI to detect contralateral disease in women with breast cancer.

The Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) aims to use the Onco*type* DX™ assay to determine the most appropriate therapy with the fewest side effects for patients with early stage breast cancer. Oncotype DX™ is a diagnostic tool developed by Genomic Health, Inc. in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP). This tool quantifies the likelihood of disease recurrence in women with early stage breast cancer and

assesses the likely benefit from certain types of chemotherapy.

Investigators searching for novel genetic prognostic markers for breast cancer recently found an association between polymorphisms in the gene SIPA1 and poor outcome in women with this disease. Another study found that prediction of breast cancer outcome by tumor p53 status is dependent on a mutation in the MDM2 oncogene. Researchers are also studying gene signatures to identify highly aggressive and less aggressive cancers. Investigators have demonstrated an inherited susceptibility to the development of visceral metastases in patients with breast cancer. Further evidence suggests that the genetic factors responsible for inherited risk for metastases may significantly contribute to the characteristic gene expression profiles that predict lung metastasis. This cutting-edge research could lead to novel prognostic markers to aid health care providers in patient management and may provide targets for new drug development.

Treatment

The NCI supports research on a range of treatments for breast cancer, including antihormone adjuvant therapy. Researchers are exploring ways to improve and extend the effectiveness of tamoxifen therapy, understand drug interactions, combat tamoxifen resistance, and identify alternative therapies for breast cancer. Current regimens of tamoxifen treatments are effective for five years, after which tumors develop resistance to the drug. Researchers have shown that small dosages of disulfide benzamide compounds can reverse tamoxifen resistance in human breast carcinoma cell lines and in *in vitro* and *in vivo* xenograft models. This is the first report of the ability to reverse tamoxifen resistance.

A new SPORE study has shown that some women taking tamoxifen may not receive the intended benefit due to genetic differences in the way tamoxifen is metabolized. Genetic polymorphisms and many commonly administered drugs, such as selective serotonin reuptake inhibitors, can affect the activity of an enzyme called cytochrome CYP 2D6, which has been shown to activate tamoxifen's therapeutic effect. Women with factors that impaired CYP2D6 metabolism had significantly shorter time to disease recurrence and worse disease-free survival compared with women who metabolized the drug normally.

Aromatase inhibitors (AIs) are compounds that suppress estrogen levels by inhibiting an enzyme necessary for estrogen production. A meta-analysis that combined data from three randomized clinical trials suggests that, for postmenopausal women with hormone-sensitive early-stage breast cancer, switching to the AI, Arimidex® (anastrozole) after two to three years on tamoxifen significantly reduced the occurrence of contralateral breast cancer.

Other clinical studies are assessing anastrozole vs. tamoxifen for adjuvant treatment of ductal carcinoma in situ. Ongoing research is investigating anastrozole with or without fulvestrant (Faslodex®) as a first-line therapy in postmenopausal women with metastatic breast disease. And still other research is comparing the safety, acceptability, and side effects of letrozole (Femara ®) vs. placebo in postmenopausal women at increased risk for breast cancer recurrence.

The NCI also supports research on conventional chemotherapies. Research has shown that postoperative chemotherapy can improve outcomes in women diagnosed with ER-negative, node-negative breast cancer. More recently, NSABP investigators reported that benefits from postoperative chemotherapy with either cyclophosphamide plus methotrexate and 5-fluorouracil or doxorubicin with cyclophosphamide were greater in younger patients. Also, the recurrence-free survival benefit was greater for premenopausal women. However, another study showed that, although women over age 65 experience more treatment-related mortality, the benefits of disease-free and overall survival were similar for older and younger women who received adjuvant chemotherapy.

The NCI is sponsoring a clinical trial for breast cancer treatment to compare the effectiveness of four different treatment schedules using the drugs doxorubicin, cyclophosphamide, and taxane in treating patients who have undergone surgery for breast cancer. Preliminary results show that no one schedule was more effective than another. Results from a secondary analysis are expected in 2007.

The NCI supports preclinical research to identify potential molecular targets for cancer therapy. Investigators recently found that Gleevec™ invokes tumor regression in a mouse

model of mammary tumors with high levels of c-kit expression. A study using a different mouse model found that the proteasome inhibitor, bortezomib (Velcade®), significantly sensitizes certain human tumor cells to tumor necrosis factor-a-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis. The combination of these two agents appeared to be superior to either agent alone. Medroxyprogesterone acetate, a progestin that has been tested as a treatment for advanced breast cancer has been found to elevate expression of the Nm23-H1 metastasis suppressor gene in hormone receptor-negative metastatic human breast carcinoma cell lines, thereby reducing metastatic colonization. This indicates a possible treatment benefit for the subset of patients with hormone receptor-negative breast cancer.

Researchers report that patients with high-risk breast cancer treated with radical mastectomy and adjuvant chemotherapy were more likely to survive if they also had localized radiation treatment. 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.

In 2006, the U.S. FDA expanded the approved use of Herceptin®, a monoclonal antibody that binds to HER2, for the treatment of HER2-positive breast cancer after lumpectomy or mastectomy. Two studies leading to this approval were conducted by NCI-sponsored Cooperative Groups. The studies closed early after showing that women who received Herceptin combined with chemotherapy had 53 percent fewer relapses and a significant improvement in overall survival for up to three years after surgery. Herceptin is also FDA approved for the treatment of metastatic breast cancer.

Preliminary clinical trial results reveal that the antiangiogenesis drug, bevacizumab (Avastin®), can slow progression of recurrent or metastatic breast cancer when it is combined with the chemotherapy drug, paclitaxel (Taxol). Avastin is already approved by the FDA to treat colorectal cancer when combined with chemotherapy. 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.

Researchers supported by the NCI preclinical research programs are helping to develop novel compounds that may be effective for breast cancer treatment. For example, compounds under investigation inhibit various kinases, tumor growth factors, prostaglandins, or angiogenesis factors. Some compounds cause histone deacylation, immune activation. Others are microtubule agents.

The NCI supports research to explore the uses of imaging to monitor therapy. One study is examining use of dynamic contrast enhanced MRI to monitor the effects of Avastin on anti-angiogenesis and the use of optical imaging for sentinel node detection. Investigators also have developed a molecular probe for *in vivo* PET monitoring of HER2 expression. A clinical trial is using contrast-enhanced MRI to identify molecular and imaging characteristics for the selection of patients most likely to respond to novel therapies that could be tested before or with standard therapies

Two new studies suggest that women receiving certain breast cancer treatments should have their cardiac health monitored. One study reported that long-term Herceptin use appears to be safe, but some patients will develop cardiac toxicity. The second study reported that irradiation of the left breast was not associated with an increased mortality from cardiac disease for up to 20 years after treatment, but it was associated with a higher rate of coronary artery disease and myocardial infarction compared with treatment of the right breast.

One of the more troubling adverse treatment effects of breast cancer is lymphedema. A team of researchers is evaluating the use of strength training as a means to prevent this disorder in patients treated for breast cancer. A second study is investigating the risk factors, development, progression, regression, and fluctuations of lymphedema, as well assessing quality of life measures.

Cancer Control, Survivorship, and Outcomes Research

The NCI supports research to discover better ways of communicating information about breast cancer. 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 Centers of Excellence in Cancer Communications Research (CECCR) includes research exploring ways of communicating risk about tamoxifen prophylaxis to women at high risk for breast cancer.

The NCI also works with partners to develop and distribute accurate and timely information on breast cancer and other important cancer-related health messages. In 2005, DHHS and the NCI launched a consolidated Department-wide information source on breast cancer on one Web site at http://www.hhs.gov/breastcancer. Other resources include a new, free educational video, *Moving Beyond Breast Cancer*, for women finishing breast cancer treatment. The 23 minute video features vignettes of women in different life stages who share their concerns and experiences. In 2005, producers for CBS-TV's soap opera, *As the World Turns*, developed two story lines with scientific feedback from the NCI. One involved a main character with breast cancer, and another involved a pregnant teen who smokes. Public service announcements featuring stars from the shows addressed mammography and teen smoking and pregnancy.

Investigators tested the effect of a lay health advisor intervention on mammography use by low-income women in a tri-racial, rural population in North Carolina. At followup, the women in the lay health advisor group had significantly better belief scores, reported reduced barriers to followup, and were more likely to have received a mammogram than women in the comparison group. In a study based in New York City, women in underserved communities who were contacted by phone by trained counselors had higher screening rates for mammography, Papanicolaou (Pap) testing, and colon cancer testing.

The NCI Center to Reduce Cancer Health Disparities (CRCHD) is administering the development of an innovative Patient Navigator Research Program that focuses on four cancers for which screening tests are available: breast, cervical, prostate, and colorectal. Patient navigators are trained, culturally sensitive health care workers who provide support and guidance throughout the cancer care continuum. Eight participating research institutions will provide navigators to help patients and their families manage cancer diagnoses and overcome common barriers to obtaining timely and appropriate cancer care and treatment. More information on the Patient Navigator Research Program is available at http://crchd.cancer.gov/pnp/pnrp-index.html.

The NCI reissued the Long-term Cancer Survivors Research Initiative in 2005. The research supported under this initiative addresses the full range of domains affected by cancer and its treatment (physical, psychosocial, behavioral, and economic) in long-term survivors. The initiative focuses on understudied areas and gaps in research.

Researchers from the WHI Observational Study followed a cohort of breast cancer survivors for 5.1 years and monitored for first-event bone fractures. Compared with a reference group of women, those who had been treated for breast cancer reported a higher incidence of bone fractures.

Health Disparities

Although white women have the highest rate of breast cancer incidence, black women have the highest death rate of all races from the disease. The NCI's *Annual Report to the Nation on the Status of Cancer 1975-2003, Featuring Cancer among U.S. Hispanic/Latino Populations* reported that Latinos have lower incidence rates than non-Hispanic whites (NHW) for breast cancers, but they are less likely than the NHW population to be diagnosed with localized stage cancers. A recent study retrospectively analyzed data from women who had been treated with mastectomy and either adjuvant or neoadjuvant systemic therapy at the M.D. Anderson Cancer Center between 1975 and 2000. The study found that, among women receiving the same treatment regimen, black women were more likely to have larger, later stage tumors and lower survival rates than Hispanic and white women. Research is needed to determine how to improve outcomes for black patients by understanding and addressing tumor biology.

A study using SEER data, as well as clinical and administrative databases, concluded that age is an independent risk factor for

receipt of non-standard cancer therapies. The investigators found that women aged 75 and older were more likely to receive nonstandard primary tumor therapy than younger women. Additionally, black women were less likely to be prescribed tamoxifen, and Asian women were more likely to undergo breast conserving surgery than were white women. Another study found that use of evidence-based treatment guidelines were significantly lower for patients who depend on Medicare or Medicaid alone for insurance. Black patients with Medicare were the least likely to receive recommended therapy.

Researchers seek to identify potential biological factors contributing to the lower breast cancer incidence rates coupled with higher breast cancer mortality rates observed in black women compared with corresponding rates observed in white women. Research includes studies to understand hormonally nonresponsive breast cancers, including ER-positive and epidermal growth factor receptor (EGFR) overexpressing breast cancers in black women.

Cervical Cancer

An estimated 11,150 cases of invasive cervical cancer are expected to be diagnosed in the U.S. in 2007, and 3,670 women are expected to die from this disease. Incidence and mortality rates have decreased steadily over the past five decades, largely due to the widespread use of the 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.

The NCI supports a SPORE on cervical cancer research, which is located at the Johns Hopkins University School of Medicine. This SPORE focuses on developing better screening, prevention, and therapeutic tools. It has a screening project in rural India and multiple interactions with the NCI Rapid Access to Intervention Development (RAID), intramural programs, and outside companies, foundations, and universities for the development and testing of novel therapeutic and preventative agents.

Risk Factors

Although oncogenic HPV infections are common and usually clear within one to two years, infection with certain HPV subtypes is now recognized as the major cause of cervical cancer. A group of approximately 15 HPVs cause virtually all cases of cervical cancer worldwide, with HPV types 16 and 18 accounting for approximately 70 percent of all cases.

Investigators have identified a possible link between immune response and development of cervical cancer. They showed that combinations of mutations in two genes associated with immune response, HLA and KIR, may influence a woman's susceptibility to developing precancerous lesions after HPV infection. Mutation combinations that appeared to confer resistance to lesion development were associated with inhibition of natural killer (NK) cell activity. Combinations that seemed to confer susceptibility were associated with activation of NK cells. Further research is needed to investigate the role of the inflammatory process and NK cells in the development of cervical cancer.

The NCI is supporting large, population-based cohort studies, including the Guanacaste Study of HPV Natural History in Costa Rica and the Portland Kaiser Permanente cohort study in the U.S., 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.

The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) will comprehensively identify and validate biomarkers for each progressive stage of cervical neoplasia (normal, HPV-infected, precancer, cancer). The investigators hope to develop a new set of biomarkers that can distinguish women at highest risk of cervical cancer from those with benign HPV infection.

The NCI continues to follow cohorts of women and their offspring exposed to DES during pregnancy. So far, analyses of SEER data show no excess risk of cancer overall in DES-exposed offspring when compared with the general population. Data from the Third Generation Study, which is assessing DES-related cancer risk in women whose mothers were exposed to DES *in utero*, show no effects of DES on age at menarche or menstrual irregularity. The NCI provides online information on DES references at http://www.cancer.gov/cancertopics/des.

The risk factors for rare forms of cervical cancer, such as adenocarcinoma and adenosquamous carcinoma, are not as well defined as the risk factors for more common squamous cell carcinoma. The multicenter Cervical Adenocarcinoma Case-Control Study is examining the role of potential risk factors for development of rare histological forms of cervical cancer. A total of 595 women have responded to a detailed risk factor questionnaire and had blood and cervical specimens collected for HPV testing and other bioassays of interest. Another recent study shows that HPV infection is a risk factor for development of cervical adenocarcinoma.

Prevention

The NCI and its partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. In June 2006, the FDA approved the use of a new vaccine, GardasilTM, made by Merck and Company, Inc. This vaccine targets four HPV types: 6, 11, 16 and 18. For women who had no evidence of previous infection, the vaccine was 100 percent protective against development of persistent infection or cervical abnormalities associated with HPV 16 or 18, and it protected against genital warts caused by HPV 6 and 11. The vaccine is based on laboratory research and technology developed at the NCI.

The NCI is conducting a randomized, controlled Phase III trial of a vaccine developed by Glaxo-Smith-Kline to prevent HPV 16 and 18 infections and their associated cervical lesions. The vaccine is based on virus-like particle technology developed by NCI intramural investigators. Recruitment is complete, and the trial is underway in an area of Costa Rica with exceptionally high rates of cervical cancer. The trial will also evaluate potential prophylactic protection against other HPV subtypes, possible therapeutic effect in women previously infected with HPV, vaccine durability, underlying biological/immunological mechanisms of protection, and other important public health issues.

A small prospective study recruited a sample of women new to sexual intercourse. Those who used condoms 100 percent of the time were 70 percent less likely to develop HPV infection than women who used condoms less than 5 percent of the time.

Another group of researchers discovered that carrageenan, a compound found in a variety of food products, cosmetics, and sexual lubricants, is a potent inhibitor of HPV infection. If proven safe and effective in a clinical trial, sexual lubricants containing carrageenan could complement the recently approved HPV vaccine by preventing infection by HPV subtypes not targeted by the vaccine.

Early Detection, Diagnosis, and Prognosis

Research funded by the NCI and others has demonstrated that detection of DNA from HPV 16 and HPV 18 predicts increased risk of cervical precancers and cancers that may develop up to several years following testing. The NCI-funded ASCUS-LSIL Triage Study (ALTS) investigated the clinical management of low-grade cervical cytologic abnormalities. The findings showed that HPV DNA testing can be used to triage patients diagnosed with atypical squamous cells of undetermined significance (ASCUS) but not low-grade squamous intraepithelial lesions (LSIL). HPV DNA negativity after ASCUS diagnosis implies very low risk of cervical precancer or cancer. The study found that a single colposcopy with biopsy, although previously considered the gold standard for diagnosis, detected only about two-thirds of high-grade lesions. Increasing the number of biopsies improved the sensitivity of the procedure. The ALTS Immunology Study is prospectively identifying biomarkers associated with a permissive vs. protective immune response to low-grade cervical lesions. Additional information on ALTS can be found online at http://www3.cancer.gov/prevention/alts/index.html.

Investigators have found that amplification of the human telomerase gene, TERC, is

a consistent aberration in cervical adenocarcinomas and may provide an objective genetic test for the assessment of glandular cells in Pap smears and hence the diagnosis of this rare form of cervical cancer. Other research has shown that an assay to detect genomic amplification of TERC in Pap smears predicts the development of cervical cancer from early to later stage lesions.

Treatment

In 2006, the FDA approved the use of topotecan hydrochloride (Hycamtin®) in combination with cisplatin for treatment of late-stage cervical cancer for women in whom surgery or radiation therapy is not likely to be effective. In clinical trials, this treatment improved survival from approximately 6.5 to 9.4 months, but it had serious side effects, including a drop in white blood cells and platelets. Topotecan hydrochloride was already approved for treatment of ovarian and small-cell lung cancers.

The NCI also supports research on side effects of treatments for cervical cancer. Researchers are testing interventions to alleviate or prevent side effects, including treatment-induced anemia and quality of life changes.

Cancer Control, Survivorship, and Outcomes Research

A recent analysis of responses to the Health Information National Trends Survey (HINTS) showed that only 40 percent of respondents had heard of HPV, and less than half of those were aware of the virus's connection to cervical cancer. Awareness was lowest among women who were older, less educated, or less exposed to health information. The researchers note that consistent information about HPV, its link to cervical cancer, and how to prevent and detect it needs to be provided before a woman becomes infected.

The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, sociological, and biomedical research on the interrelationships among 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.

Several studies are underway to assess sexual function and general quality of life for women receiving treatment for different stages of cervical cancer. The NCI is supporting about a dozen studies that address the social, emotional, and interpersonal impact of cancer and its treatment on sexual functioning in survivors and their partners. This research will provide information on how best to counsel survivors and their partners on what to expect after treatment and ways to minimize some of the more distressing personal costs of disease treatment and cure.

Health Disparities

The NCI CRCHD has an ongoing program to address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas. Women most affected include black 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. In 2005, the CRCHD released the report, *Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities*. The authors propose intensifying outreach to underserved women, stressing the importance of a "medical home" to ensure continuity of care, increased availability of patient navigators, and more female and minority health care providers. The report also called for improved insurance coverage, linguistically accessible information services, and optimized HPV testing and vaccine development.

The CRN reported in 2005 that more than half of cervical cancer cases among 833 women in seven health maintenance organization managed care plans were attributable to lack of Pap testing. Women older than 39 and women living in a high-poverty area or with low educational levels were more likely to have not received a Pap test. Research to improve the use and effectiveness of cervical cancer screening includes a recent clinical trial which compared a single-visit approach to cervical cancer screening and treatment vs. the standard of care (i.e., Pap testing and referral for a followup visit) in an underserved population. Women in the single-visit group were

significantly more likely to receive definitive treatment within six months of diagnosis of high-grade lesions.

The NCI's CIS, in partnership with the CDC, the ACS, and the U.S. Department of Agriculture, is conducting a pilot project called TEAM-UP: Cancer Screening Saves Lives. This project is using evidence-based interventions to increase participation in cervical and breast cancer screening programs among never and/or rarely screened women in eight states with persistently high incidence and mortality rates of cervical and breast cancer.

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's CRCHD is also administering the development of an innovative Patient Navigator Research Program that is focusing on four cancers for which screening tests are available: breast, cervical, prostate, and colorectal. Additional information on the navigator program is available online at http://crchd.cancer.gov/pnp/pnrp-index.html and in the breast cancer section of this report.

Researchers have found that, in a population of women positive for HPV 16 and HPV 18, white women and black women tended to have different genetic variants of these viruses, termed European and African variants, respectively. Investigators suggest the need for research to examine possible mechanisms of variant-specific immune evasion and potential therapeutic implications.

Ovarian Cancer

In 2007, approximately 22,430 women in the U.S. are expected to be diagnosed with ovarian cancer, and approximately 15,280 are expected to die of the disease. Between 1985 and 2003, incidence rates decreased by 0.7 percent per year. Ovarian cancer is responsible for the highest mortality rates of all gynecologic cancers. Incidence and mortality rates are highest in white women compared with other racial and ethnic groups. When detected early, ovarian cancer is highly treatable, with a five-year survival rate of 93 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 30 percent for stages with distant metastases.

The NCI's five ovarian cancer SPOREs frequently collaborate to develop prognostic, screening, prevention, and therapeutic tools for ovarian cancer. SPORE activities include identification of an optimally sensitive panel of known markers, such as CA-125, and novel markers for the early detection of ovarian cancer in conjunction with transvaginal ultrasound. Additional information on these SPOREs is available online at http://spores.nci.nih.gov/current/ovarian/ovarian.html.

The NCI supports other research on ovarian cancer. Examples of this research include clinical trials of targeted therapy with vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) blockers in combination with chemotherapy, gene therapy in combination with chemotherapy, and development of therapies that target the phosphatidylinositol 3 kinase (PI3K) pathway, which is frequently mutated in ovarian cancer. Another project aims to develop strategies to identify ovarian cancer patients least likely to respond to modern platinum/taxane-based treatments and to develop therapeutic strategies to attack cancer cells in these patients.

Biology

The NCI and the NHGRI support The Cancer Genome Atlas (TCGA). The TCGA pilot will assess the feasibility of developing a useful atlas of the changes in the human genetic blueprint associated with all types of cancer, beginning with ovarian, lung, and brain cancers.

A study using DNA microarray technology helped to clarify the relationship between low malignant potential (LMP), low-grade, and high-grade serous ovarian tumors. The study suggests that LMP tumors are not early precursors of aggressive ovarian cancer, as had been suspected. These tumors may be part of an entirely different class of tumors. Researchers also showed that low-grade serous tumors are more similar to LMP tumors than to high-

grade serous tumors. This finding suggests that women with low-grade tumors may benefit from different therapies than those given to patients with high-grade tumors.

Several new mouse models are useful for elucidating the biology of ovarian cancer to inform the development of potential ovarian cancer treatment strategies. For example, NCI-MMHCC researchers found elevated levels of the protein COX1 in three mouse models (each involving changes to different genes) of human epithelial ovarian cancer (EOC). However, the level of the related COX-2 protein, which is associated with a variety of cancers, was not elevated. Specific inhibition of COX-1 led to significant tumor reduction in all three models. The NCI-MMHCC has also developed mouse models for endometroid ovarian cancer, a subtype of EOC. Another model was designed to permit molecular characterization of BRCA1-associated EOC.

In another study, researchers identified and characterized a distinct subpopulation of ovarian cancer stem-like cells in a genetically engineered mouse cell line. Researchers are using the mouse cells to study the role of stem-like cells in recurrent ovarian cancer and to design new targeted therapeutic agents. They have shown that these putative tumor stem cells are sensitive to a glycoprotein called Mullerian Inhibiting Substance (MIS), and that MIS is able to enhance subclinical doses of standard chemotherapy for EOC and inhibit growth of both human and mouse EOC cell lines.

Mouse models are also used to inform potential strategies for cancer detection. Optical imaging of mouse models is helping researchers to locate microscopic intraperitoneal metastases, which commonly recur after surgery because small tumor foci escape detection within the complex anatomy of the peritoneal cavity and mesentery. Researchers are working toward bringing this technology into the clinic.

An association between chronic behavioral stress and increased tumor burden and more invasive growth of ovarian carcinoma cells was identified using yet another mouse model. The effects of stress seemed to be mediated by angiogenic processes, providing clues for the development of cancer treatment strategies.

Risk Factors

In the U.S., approximately one woman in 70, or 1.4 percent, will develop ovarian cancer during her lifetime. Researchers are investigating potential mechanisms by which reproductive, demographic, and lifestyle factors affect risk of ovarian cancer. Oral contraceptive use, having had at least one full-term pregnancy, and having breastfed are associated with a reduced risk of ovarian cancer. Tubal ligation and hysterectomy may be associated with a decreased incidence of ovarian malignancy. HT use in postmenopausal women may be associated with an increased risk of developing ovarian cancer. However, the single greatest risk factor is a family history of the disease. Three inherited ovarian cancer susceptibility syndromes have been described: (1) familial sitespecific ovarian cancer, (2) familial breast/ovarian cancer, and (3) Lynch II syndrome (a combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers). It is believed that inherited mutations in the BRCA1 or BRCA2 genes cause 5 to 10 percent of ovarian cancers.

Researchers who evaluated self-reported data from a large cohort study found that women aged 50 to 71 who took unopposed estrogen for 10 or more years had a significantly increased risk of ovarian cancer, whereas women who took unopposed estrogen for a shorter period had no increased risk. Also, women with intact uteri who took estrogen plus progestin were about twice as likely to develop ovarian cancer as women with intact uteri who never used hormone therapy.

The Breast and Ovarian Cancer Family Registries comprise an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a focus on the genetic and molecular epidemiology of breast and/or ovarian cancers.

Prevention

Women who are at high risk of ovarian cancer because they carry mutated BRCA1 and BRCA2 genes can reduce the risk to reproductive organs by about 60 percent by having preventive surgery to remove their ovaries and fallopian tubes, according to the largest prospective study yet done on this issue. The NCI has completed enrollment of 2,300

women to a multicenter clinical trial that will further quantify the extent of breast and ovarian cancer risk reduction after preventive removal of the ovaries and fallopian tubes in women at high risk for ovarian cancer. The study will also assess quality of life and incidence of non-cancer diseases related to premature menopause. Researchers will evaluate a novel approach to ovarian cancer screening based on quantitative assessment of changes in the tumor marker, CA-125, over time. Study investigators are developing and validating a model of medical decisionmaking related to the choice of surgery vs. screening.

Early Detection, Diagnosis, and Prognosis

Researchers conducting a national, multicenter clinical trial will collect blood samples from patients after successful treatment of advanced ovarian cancer. These samples will be used to develop proteomic technology to detect recurrent ovarian cancer well before symptoms appear. The long-term goal of this project is to develop a means of detecting early-stage ovarian cancer.

Another experimental blood test may one day help diagnose ovarian cancer and mesothelioma. The test measures levels of mesothelin, a protein shed into the blood of patients with these cancers. Analyses showed that mesothelin levels were elevated above control levels in 14 out of 21 patients with ovarian cancer and in 40 out of 56 patients with mesothelioma. Other observations suggest that this blood test may be useful for monitoring disease progression. Further research is needed to validate these initial findings.

The NCI is supporting the National Ovarian Cancer Early Detection Program: Screening and Genetic Study. This multisite clinical trial seeks to identify effective screening and genetic testing methods for finding 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. Additional information is available online at http://www.clinicaltrials.gov/ct/gui/show/NCT00005095.

The NCI provides support for the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial. Preliminary results from the ovarian cancers screening component of the PLCO trial were released in November 2005. Screening with transvaginal ultrasound and a blood test for the tumor marker CA-125 did find tumors but also yielded many false positive results. Based on these findings, the investigators concluded that these tests cannot currently be recommended for widespread screening in the general population. Several studies are using blood samples collected from asymptomatic PLCO participants who later developed ovarian cancer. These studies are conducting research on biomarkers that could be developed into diagnostic tests for detection of early stage ovarian cancer. The PLCO has also provided DNA samples from thousands of patients and healthy controls for whole genome scanning to identify breast cancer susceptibility genes and provide a better understand the biological basis of breast cancer.

Treatment

The treatment of ovarian cancer is evolving rapidly as results emerge from ongoing clinical trials. Standard postsurgery chemotherapy for newly diagnosed ovarian cancer usually consists of treatment with a platinum-based drug (e.g., carboplatin or cisplatin) in combination with either alkylating agents or paclitaxel. Patients whose disease recurs more than six months after completion of chemotherapy are usually retreated with a platinum-based drug.

In January 2006, the NCI issued a rare clinical announcement to raise awareness about intraperitoneal (IP) chemotherapy (delivered by a catheter to the abdominal cavity) for ovarian cancer. The announcement followed striking clinical trial findings that women with ovarian cancer who received intravenous (IV) and IP chemotherapy after removal of most tumor tissue lived on average 16 months longer than women who had surgery and IV chemotherapy alone. Before this announcement, IP chemotherapy was widely regarded as old technology and only given to about 1 percent of women with ovarian cancer, in part because of increased toxicity associated with the delivery method. However, even though patients in the IP/IV group experienced more complications, most problems were manage-

able and transient. Both groups reported a similar quality of life one year after treatment.

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 Velcade, docetaxel (Taxotere®), erlotinib (Tarceva®), gemcitabine (Gemzar®), ixabepilone (BMS-247550), liposomal doxorubicin, nitrocamptothecin, oxaliplatin (Eloxatin®), sorafenib (BAY 43-9006), Avastin, TLK286, and topotecan. In 2006, clinical trial researchers reported that patients with recurrent ovarian cancer treated with a combination of gemcitabine plus carboplatin lived a median of 2.8 months longer than those who received carboplatin alone. Both groups of women experienced about the same quality of life. Other 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.

In preclinical research using a mouse model for mesothelin-bearing tumors, the combined administration of paclitaxel and the immunotoxin-SS1P was much more effective than either treatment alone and caused long-lasting complete remission in the mice. The SS1P targets the protein mesothelin, which is present in 70 percent of ovarian cancers. Paclitaxel is known to be effective against ovarian cancer, and prior research has shown some treatment effect of SS1P alone in a Phase I trial that included patients with ovarian cancer. The investigators hypothesize that the synergistic effects of paclitaxel and SS1P will work better than either agent alone.

According to a May 2005 report, removing the aortic and pelvic lymph nodes during surgery for advanced ovarian cancer does not improve overall survival. On average, women receiving lymphadenectomy surgery had a seven month longer disease-free survival but also experienced more complications associated with the surgery.

Cancer Control, Survivorship, and Outcomes Research

In 2006, the NCI updated its booklet, *What You Need to Know about Ovarian Cancer*. This booklet answers patients' questions about symptoms, diagnosis, staging, and treatment. It is available online at www.cancer.gov/publications.

The American Society of Clinical Oncology (ASCO) has released guidelines for addressing fertility preservation options for patients before cancer treatment. The ASCO convened an expert panel, which noted that many oncologists either do not discuss the possibility of treatment-related infertility or do so only suboptimally. The panel also found that fertility preservation is of great importance to many patients, and properly addressing the issue was a positive factor in patients coping emotionally with cancer. The NCI supports research on this topic and, in 2005, provided funds to researchers at M.D. Anderson Cancer Center for a scientific workshop on *Parenthood after Cancer: Today's Options, Tomorrow's Hopes*.

Researchers analyzing SEER data on women with ovarian cancer aged 65 and older found that women treated by a gynecologic oncologist had marginally better survival rates than those treated by general oncologists and markedly better outcomes compared with patients treated by general surgeons. A companion study found that specialized training improved patient outcomes more than surgeon volume (i.e., the number of relevant surgeries performed by the surgeon).

Endometrial Cancer

Cancer of the *corpus uteri*, or endometrium, is the fourth most common invasive cancer among women in the U.S. An estimated 39,080 American women will be diagnosed with uterine cancer in 2007, and approximately 7,400 will die from the disease. The incidence of endometrial cancer declined from 1975 to 1988, increased slightly over the next decade, and again has begun to decline. The average incidence rate for white women was 24.5 per 100,000 from 1999 to 2003; the average incidence rate for black women was much lower, at 19.7 per 100,000. The average mortality rates show the opposite pattern, with the death rate for white women at 3.9 per 100,000 and for black women at 7.1 per 100,000, nearly double the rate for white females.

The Gynecological Cancer SPORE at the University of Texas M.D. Anderson Cancer Center 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 SERMs, such as tamoxifen, raloxifene, and a new third-generation SERM, Arzoxifene, in the epithelial and smooth muscle compartments of the uterus.

Biology

Researchers are developing mouse models to study molecular genetic abnormalities that may be predictive of progression of precursor lesions. Because of the present inability to predict which precursor lesions may progress and the morphologic ambiguities of distinguishing between complex atypical hyperplasia (CAH) and uterine endometrioid carcinoma (UEC), numerous women undergo hysterectomy for benign, non-invasive disease. A more thorough understanding of the differences between CAH and UEC and the role of both hormonal and genetic factors on the development and progression of endometrial tumorigenesis would substantially improve the diagnosis and management of women with endometrial lesions.

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 Web site can be found at http://pluto3.nci.nih.gov/tissue/default.cfm. This resource can assist researchers in identifying sources of tissue.

Risk Factors

Scientists have found significant increases in endometrial cancer risk for women who used estrogen and progesterone, including women who used continuous estrogen plus progestin regimens. Elevations in risk persisted at least 10 years after last use. These results suggest the need for continued monitoring of long-term effects of unopposed estrogen and estrogen plus progestin menopausal hormone therapies. Other factors associated with increased risk for endometrial cancer include personal history of breast cancer, tamoxifen use, obesity, age, lack of physical activity, hereditary nonpolyposis colon cancer (HNPCC or Lynch syndrome), diabetes, and other medical conditions. However, underlying 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. Tamoxifen, which is used in the prevention and treatment of ER-positive breast cancer, has also 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 AIs, that can be used alone or in combination with tamoxifen for treatment of hormone-dependent tumors are being investigated.

Prevention

NCI prevention studies focus 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. An ongoing Phase II randomized study is examining the role of progestins (medroxyprogesterone) vs. low-dose ethinyl estradiol and norgestrel for the prevention of endometrial cancer in HNPCC patients.

Early Detection, Diagnosis, and Prognosis

Researchers are studying the PTEN tumor suppressor gene to establish whether it has clinical cancer predicative value for endometrial cancer. PTEN is altered very early in endometrial carcinogenesis and displays decreased protein expression in 75 percent of premalignant and malignant endometrioid lesions. The

goal is to develop a strategy for early detection and chemoprevention of endometrial cancer.

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. In November 2006, the NCI joined with the United Kingdom Cancer Research Institute and Medical Research Council to co-sponsor a state-of-the-science meeting for treatment issues in endometrial cancer. Investigators from clinical trials groups around the world identified 14 key trials on which they hope to collaborate.

The NCI-funded Gynecologic Oncology Group (GOG) conducts research focused on women with pelvic malignancies, including endometrial cancer. In a Phase III GOG clinical trial, postsurgical adjuvant chemotherapy with cisplatin and doxorubicin improved survival by 33 percent in women with advanced endometrial cancer compared with women treated with standard whole abdominal radiation. Because toxicity can be a problem with this chemotherapy regimen, GOG is conducting a Phase III trial to investigate the better tolerated carboplatin and paclitaxel therapy. Additional information on the GOG is available online at http://www.gog.org/.

Results of a retrospective analysis using SEER data from more than 21,000 women with early-stage endometrial cancer demonstrate a significant survival benefit with adjuvant radiation therapy (RT) in subsets of women with high-risk disease. Overall survival and relative survival were improved in women with grade one, three, and four tumors that had spread into the layer of muscle around the uterus (stage IC). Further investigation is needed to determine which patients with early-stage disease are at highest risk for recurrence after surgery and how best to treat them.

The NCI is conducting research on hormone therapies for endometrial cancer. A Phase II pilot study is comparing the efficacy of medroxyprogesterone in patients with progesterone receptor-positive vs. progesterone-receptor negative endometrial adenocarcinoma of the uterine corpus.

The NCI supports studies comparing different chemotherapies, alone or in combination, 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, Herceptin, Avastin, sorafenib, temsirolimus (CCI-779), and the drug 852A for treating endometrial cancer. Side effects of therapy and quality-control issues in radiation equipment are also being investigated.

Health Disparities

Previous studies have suggested that the disparities in survival for black women compared with white women with endometrial cancer were due to differences in treatment. However, a recent retrospective analysis of data from four GOG randomized treatment trials found that in a setting where all patients received equal care, black women had a 25 percent greater chance of dying than white women with the same diagnosis. A second study found differences in tumor gene expression patterns between black and white women with advanced stage endometrial cancer. These studies suggest that, while treatment disparities should still be investigated, socioeconomic, biologic, and cultural factors should also be addressed to decipher the causes of this health disparity.

Lung and Other Tobacco-related Cancers

Tobacco use is the leading preventable cause of premature death in the U.S. Each year, more than 440,000 Americans die of tobacco-related disease, accounting for one in every five deaths. Cigarette smoking is responsible for more than 30 percent of cancer deaths annually in the U.S. Research shows that tobacco use causes an increasing number of cancers of particular concern to women, including lung, cervical, and ovarian cancers. Scientific evidence also suggests a causal relationship between smoking 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 is also a causal factor in 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 98,620 women will be diagnosed with lung cancer in 2007, and 70,880 women will die from this disease in the U.S. Although incidence and death rates in men have been declining since the early 1980s and 1990s, respectively, these rates for women continued to increase. The latest analysis of SEER data now shows an attenuated increase in mortality rates from 1991 to 2003. A recent analysis suggests that the discrepancy in declining incidence rates between men and women largely reflects smoking prevalence from past decades. High death 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 five-year relative survival is only 2.1 percent. Black men have the highest death rates from lung cancer followed by somewhat lower rates for non-Hispanic white men. The highest lung cancer death rates occur in non-Hispanic white women with slightly lower rates found in black women.

The Women, Tobacco, and Cancer Working Group, a public/private partnership led by the NCI, released the report, *Women, Tobacco, and Cancer: An Agenda for the 21st Century*, in July 2004. This report is available online at http://women.cancer.gov/reports/wtobacco.shtml. The report recommends strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, evaluation, and surveillance that will contribute to reducing and ultimately eliminating the harmful health effects of smoking in women. The report has been disseminated to the global tobacco research and advocacy communities. In response, the Tobacco Research Network on Disparities (TReND) initiated the Low SES Women and Girls Project in 2004 to strategically address and examine the effects of multiple tobacco control policies on diverse populations of low socioeconomic status (SES) women and girls. The project aims to stimulate new research, review existing research, and, as a result of its findings, inform the development and implementation of policies and programs by practitioners that may reduce tobacco use among this population. A scientific meeting titled *Tobacco Control Policies: Do They Make a Difference for Low SES Women and Girls?* was convened in September 2005.

The NCI Lung Cancer Integration and Implementation team led to the establishment of the lung cancer program (LCP). The central focus of this program will be to support research on lung cancer biology, early detection, and treatment. The LCP will also provide resources to CISNET to improve the understanding of the impact of cancer control interventions in tobacco cessation, early detection, screening, and therapy. The LCP will also support tissue acquisition, processing, and archiving in the National Lung Screening Trial.

The Transdisciplinary Tobacco Use Research Centers (TTURCs) provide the infrastructure needed to facilitate a transdisciplinary approach to the full spectrum of basic and applied research on tobacco use to reduce the disease burden of tobacco. A group of seven TTURCs is funded by the NCI, the NIDA, and the NIAAA. TTURC researchers study a range of topics, including the etiology of tobacco use and addiction, the impact of advertising and marketing, prevention of tobacco use, treatment of tobacco use and addiction, identification of biomarkers of tobacco exposure, and identification of genes related to addiction and susceptibility to harm from tobacco. Additional information on the TTURCs is available online at http://dccps.nci.nih.gov/tcrb/tturc.

The NCI currently funds seven lung cancer SPOREs. The Lung SPORE at the University of Pittsburgh Cancer Institute focuses on improving detection and treatment of lung cancer and understanding the mechanisms of women's susceptibility to this disease. Researchers at this SPORE are investigating the role of ERs in lung cancer in women. A clinical trial is planned to explore possible protective effects of administering ER antagonists to lung cancer patients. Additional information on the lung SPOREs is available online at http://spores.nci.nih.gov/current/lung/lung.html.

Biology

Among those who smoke, women are more likely than men to get more aggressive forms

of lung cancers. Also, among people who have never smoked, women are more than twice as likely as men to develop lung cancer. These patterns suggest biological differences in the way lung cancer develops in men and women. A Southwest Oncology Group (SWOG) study will investigate why women seem to get a different type of lung cancer than men and at an earlier age, especially if they have never smoked. The study will also seek to better understand the factors that cause lung cancer in both men and women who do not smoke.

Both the NCI and the NHGRI support The Cancer Genome Atlas (TCGA). A TCGA pilot study will assess the feasibility of developing a useful atlas of the changes in the human genetic blueprint associated with all types of cancer, beginning with lung, brain, and ovarian cancers.

Risk Factors

A multicenter, case-control study of lung cancer and tobacco use is ongoing in Milan, Italy. This trial includes the collection of extensive questionnaire and biospecimen data and is unique in collecting other information, including demographics, tobacco use, alcohol use, occupational exposures, diet, medical illness, and tumor tissue obtained in surgery. Investigators are now evaluating differences in expression arrays in lung adenocarcinomas, normal lung tissue, and matched lymphocytes among never smokers, previous smokers, and current smokers.

The PLCO and the Shanghai Women's Health Study are large, ongoing cohort studies that include the collection of biospecimens and questionnaire data with a focus on tobacco-related cancers. Information from these cohorts can be used in a variety of studies related to the effects of tobacco exposures. Additional information on these studies is available online at http://www3.cancer.gov/prevention/plco/ and http://epi.grants.cancer.gov/ResPort/ShanghaiWomen.html.

The NCI also supports transdisciplinary research on the interplay of behavior, chemistry, toxicology, biology, and epidemiology to determine the cancer risk potential of reduced-exposure tobacco products. Current scientific evidence is insufficient to evaluate whether these new products actually reduce the user's exposure or risk for tobacco-related diseases.

Two recent studies emphasized the health risks of exposure to secondhand smoke. One study showed that patients who had been exposed to high levels of secondhand tobacco smoke over many years did not live as long on average as patients who had been exposed to lower levels. A European study found an association between exposure to secondhand smoke and risk of lung cancer. The risk was higher among former smokers than among never smokers. Furthermore, infants who were exposed to second hand smoke were up to three times more likely to develop lung cancer as adults.

A large chemoprevention study has shown that a high intake of phytoestrogen compounds decreases the risk of lung cancer. Investigators reported that study participants who ate the most phytoestrogens reduced their lung cancer risk by 46 percent compared with those who ate the lowest amount. However, women benefited less than men, and former smokers benefited less than never smokers. The investigators cautioned that much more research is needed to prove a definitive chemoprevention effect.

Studies supported by the NCI and others have confirmed that genetic mutations associated with non-small-cell lung cancer (NSCLC) occur preferentially in certain subsets of patients, including women, patients who have never smoked, patients with adenocarcinoma, and patients of Asian descent. Two recent studies have found epidemiologic evidence of familial risk for lung cancer. Both studies found that the incidence of lung cancer was higher in family members of patients with this disease compared with family members of healthy individuals, even after eliminating the effects of smoking on risk. One study also found that family members of black patients with early-onset lung cancer are twice as likely to develop lung cancer when compared with family members of white patients with this disease. Further research is needed to identify the genetic factors contributing to lung cancer risk suggested by these findings.

Scientists are elucidating the role of proteins in the development of tobacco-related cancers to identify strategies to prevent and treat this disease. Recent studies show that activation of the protein AKT occurs early in the development of tobacco-related cancers, such as lung

cancer. This critical protein may form the basis of a decisionmaking tool to individualize care for patients with early-stage NSCLC. Another study has shown that long-term smoking cessation increases the blood levels of an important anti-inflammatory protein, CC10, which may play a role in combating the development of lung cancer. Although this study suggests that quitting smoking may lead to repair of some lung damage, further studies are needed to elucidate CC10's role in lung cancer.

Prevention and Control

A study funded in part by the NCI found that children aged 10 to 17 smoked less and displayed more favorable antismoking attitudes and beliefs when they had been recently exposed to antismoking television advertisements sponsored by state public health departments. The results show that state-sponsored advertising, while much less frequent than anti-tobacco advertising sponsored by the tobacco industry, is much more effective. Another study found that adolescents aged 10 to 14 who watched the most smoking in the movies were almost three times more likely to start smoking than their peers who watched the least amount of smoking in movies. This result was found in all regions of the country, regardless of race and ethnic group.

The importance of smoking cessation was emphasized by the recent findings of the NHLBI Lung Health Study. This study was the first to demonstrate that smoking cessation results in lower lung cancer mortality. However, results from the annual National Health Interview Survey (NHIS) show that the steady decline seen in smoking rates over the last eight years had come to a halt. The authors cited smaller annual increases in the price of cigarettes, increased tobacco industry expenditures on price discounts, and a significant drop in state tobacco control program funding as possible contributors to their findings. Furthermore, the NCI's HINTS has revealed that smokers underestimate their relative risk of lung cancer compared with nonsmokers. In addition, HINTS found that many current and former smokers incorrectly agree with several myths about smoking and health, with more than half agreeing that exercise undoes most of tobacco's negative effects.

The NCI supports a variety of culturally appropriate interventions to encourage and help tobacco users to quit smoking. The NCI and the CDC *Quit Now Challenge* of October 2006 featured inspirational stories of people who want to quit smoking. Tobacco users submitted stories in their own words about why they wanted to "quit now." In February 2006, stories were chosen from successful quitters, who were given public opportunities to share their experiences to help others quit. In November 2005, ABC-TV partnered with the NCI, the CDC, and the North American Quitline Consortium to air *Quit to Live: Fighting Lung Cancer*, a televised series of reports on smoking cessation and lung cancer prevention.

NCI publications related to smoking are available to the public and include Clearing the Air, a manual designed to help smokers quit; *Clear Horizons*, a quitting guide for individuals older than 50; the Spanish-language guide on smoking cessation, *Guia para Dejar de Fumar*; *Pathways to Freedom* for African American smokers; and Fact Sheets and FAQ, for smokers and non-smokers looking to learn about the impact of smoking. Information is also available online at http://www.smokefree.gov/info.html.

The NCI also provides resources to inform the development of effective tobacco control programs. The NCI and the CDC partnered with the Robert Wood Johnson Foundation to launch the Helping Young Smokers Quit initiative. This two-phase project has gathered information from a representative sample of youth smoking-cessation programs throughout the U.S. and will evaluate whether these programs have helped youth quit smoking. The monograph, *ASSIST: Shaping the Future of Tobacco Control* is available online at http://dccps.cancer.gov/tcrb/monographs/16/index.html. The monograph was released in June 2005 and documents models and lessons learned. It describes case studies from the eight-year American Stop Smoking Intervention Study for Cancer Prevention (ASSIST) demonstration project. The monograph provides concrete examples for building long-term capacity and positive behavioral health changes by applying these policy and media approaches. The monograph, *Evaluating ASSIST—A Blueprint for Understanding State-Level Tobacco Control*, was released in 2006. Through the International

Tobacco and Health Research and Capacity Building program, the NCI and partners support transdisciplinary research and capacity building projects that address the burden of tobacco consumption in low- and/or middle-income nations.

Researchers released a 13-year followup study of the NCI's Community Intervention Trial for Smoking Cessation (COMMIT). Researchers found that the higher quitting rates in the COMMIT intervention communities vs. comparison communities were achieved while the study was funded, but they were absent eight years after the program ended. This suggests that continued impact of tobacco control interventions require sustained funding. The study also found that quitting rates were highest in states with both strong tobacco-control policies and aggressive tobacco-control programs.

Many studies have suggested that women may have greater difficulty quitting smoking than men. A TTURC study examined gender differences in smoking cessation in a placebo-controlled trial of bupropion with behavioral counseling. The investigators found that bupropion particularly benefited men who smoked more than one pack of cigarettes per day at baseline and, conversely, women who smoked a pack or less. These findings suggest that bupropion treatment may help reduce the gender disparity in prolonged abstinence rates among lighter smokers.

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

Researchers have completed enrollment of 50,000 current and former smokers into the ACRIN and NCI-supported National Lung Screening Trial (NLST). Approximately half of the participants are women, and about 4 percent are racial/ethnic minorities. This eight 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, as well as economic consequences and other potential differences between the two screening methods. Additional information on the NLST can be found online at http://www.nci.nih.gov/nlst.

Preliminary results from the PLCO Cancer Screening Trial, which were reported in 2006, show that chest x-rays can detect lung cancer earlier, but they also produce many false-positives that cause needless extra tests. Further analysis will reveal if the group receiving screening x-rays has a lower lung cancer mortality rate than the group receiving usual care.

The recently created NCI Imaging Archive (NCIA) contains large collections of lung computerized tomography (CT) and PET scans as a research resource for software developers. This resource will enable development of algorithms for computer-aided detection and diagnosis of small lung nodules. The NCI and the NIH Biomarker Consortium are also supporting a clinical trial to evaluate PET as a biomarker for prognostic measurement of treatment-related tumor volume changes in patients with NSCLC.

Researchers are developing tests that may one day be used for clinical detection, diagnosis, and treatment planning. For example, the experimental metagene model may help predict the risk of recurrence for patients with early stage lung cancer and determine which patients would most likely benefit from adjuvant chemotherapy. A prospective study is needed to assess the model after two evaluation studies showed an overall predictive accuracy for recurrence risk of 72 percent and 79 percent. The metagene model is similar to the genomic strategy used in the TAILORx breast treatment trial. Other research suggests that testing the sputum of individuals at high risk for lung cancer to detect genes silenced by methylation is a promising screening strategy for early signs of the disease. Another promising approach to lung cancer screening involves gene profiling of cells obtained from the airway during fiberoptic bronchoscopies.

Early research is identifying other molecular signatures that may one day prove useful for detection, diagnosis, or prognosis of lung cancer. For example, investigators have

found that the increased expression patterns of certain microRNAs may be associated with poorer patient prognosis, suggesting the need for more aggressive treatment. Researchers from the International Adjuvant Lung Cancer Trial (IALT) identified lack of expression of the DNA-repair protein, ERCC1, as a possible predictor of increased survival after cisplatin-based adjuvant chemotherapy. Further studies are needed to determine whether prospective testing for ERCC1expression will predict patient response to therapy.

Treatment

The NCI supports clinical trials to improve outcomes and reduce treatment toxicity in patients with lung cancer by testing regimens of drug combinations for adjuvant chemotherapy. One study showed that adjuvant chemotherapy with cisplatin-based regimens prolongs survival in patients with resected stage II-III disease.

Investigators treating NSCLC cell lines with several chemotherapy drugs found that nicotine suppressed the cell-killing ability of each drug. The investigators stress the need to take the effects of nicotine into account when developing new treatments for lung cancer.

Two EGFR inhibitors, gefitinib (Iressa®) and Tarceva®, are used to treat some NSCLC patients. These drugs act by inhibiting the angiogenesis needed for tumor growth. Because two trials did not show that Iressa improved survival of patients with lung cancer, the FDA restricted use of this drug in 2005 to patients who are currently taking it or have previously benefited from it. Since only about 10 percent of advanced-stage NSCLC patients respond well to EGFR inhibitors, the NCI supports research to define genomic and proteomic markers for prediction of patient response to these agents. Researchers are also identifying strategies to combat acquired resistance to EGFR inhibitors in patients receiving long-term treatment with the drugs.

In 2006, Avastin in combination with paclitaxel and carboplatin was approved by the FDA for use in advanced NSCLC patients after clinical results showed that this treatment regimen improved survival. However, a preliminary analysis in a separate study suggests that female patients with lung cancer may not respond as well as male patients to Avastin. The NCI supports clinical trials of other molecularly targeted agents, including sorafenib and cetuximab (Erbitux®).

Preclinical research is yielding information about potential new targets for lung cancer therapy. Promising strategies include inhibition of the AKT protein pathway with phosphatidylinositol ether lipid analogs and inhibition of the protein ErbB3, which appears to interact with AKT to maintain proliferation and invasiveness of lung adenocarcinoma.

Prior studies have shown that chemotherapy for older patients with NSCLC is associated with some survival benefits but also with significant toxicity. However, a Phase II study has shown promising results for the drug erlotnib as well as tolerable toxicity as a first line treatment for elderly patients with advanced NSCLC. Another study showed that adjuvant platinum-based chemotherapy for elderly patients with NSCLC improves survival without an increase in treatment-related toxicity or hospitalization when they were compared with younger patients.

Health Disparities

TReND, which is supported by the NCI and the American Legacy Foundation, conducts interdisciplinary research to understand tobacco-related health disparities, translates scientific knowledge into practice, and informs 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.

In 2007, the NHIS reported that smoking prevalence among Americans with graduate degrees fell to 7.1 percent while the prevalence among those with a graduate equivalency degree (GED) was 43.2 percent. Prevalence was also higher among people living below the poverty level than among those at or above the poverty level (29.9 percent vs. 20.6 percent). NCI-supported studies are looking at the influence of SES on various aspects of tobacco use and cessation. One of the first major questions addressed by TReND is focused on the effects of tobacco control policy and women of low SES.

A large prospective study has found that both blacks and native Hawaiians had signifi-

cantly greater risks of lung cancer related to smoking compared with whites, Hispanics, and Japanese Americans. These racial and ethnic differences were greatest among those who smoked 10 cigarettes or less a day. For smoking rates as high as 30 cigarettes a day, the difference in risk among groups was minimal.

A retrospective study of 97 black patients and 184 white patients with early stage lung cancer found that black patients were far more likely than white patients to decline offered surgical therapy. However, the chances of five year survival are as high as 50 percent in patients with early stage disease who are treated with surgery; the median survival is less than one year for those who decline surgery. This and other studies suggest that factors contributing to this disparity may include a lack of trust in the health care system and a belief that surgery to treat lung cancer can actually cause the disease to metastasize.

Colorectal Cancer

It is estimated that 74,630 women in the U.S. will be diagnosed with cancer of the colon or rectum in 2007, and an estimated 26,180 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women. Black women have the highest incidence and death rates, followed by non-Hispanic white women. Colorectal cancer incidence rates have alternately risen and declined since 1975. Modest decreases in colorectal cancer 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 (API) women and lowest among black women. Lower rates of treatment with adjuvant therapy among black patients may contribute to differences in cancer survival.

The NCI supports four gastrointestinal (GI) SPOREs, which focus research on cancers of the colon, rectum, and other digestive organs. SPORE researchers are exploring ways to use knowledge about the molecular genetics of colorectal cancer to improve early detection, prevention, and management of the disease. For example, researchers are using emerging genetic insights to devise new strategies for chemoprevention.

Biology

Two research studies identified colon cancer stem cells and showed that only a small subset of tumor cells from patients with colon cancer could initiate new tumors and sustain their growth. These few cancer stem cells, when transplanted into mice, were able to form tumors that resembled the original cells in patients while other tumor cells could not. These findings suggest that targeting stem cells may be an effective strategy for preventive and therapeutic interventions.

Risk Factors

Researchers are investigating potential effects of various dietary factors on the risk for colorectal precancer and cancer. Data from the Polyp Prevention Trial show that participants who consumed the highest level of dry beans had a two-fold reduction in colorectal adenoma recurrence. A European study reported that high levels of consumption of red and processed meat are associated with an increased risk of colorectal cancer, while high levels of fish consumption are associated with a decreased risk of the disease. Researchers from the WHI reported that taking daily supplements of calcium and vitamin D for seven years did not reduce the risk of colorectal cancer in postmenopausal women. The supplements were modestly effective at preserving bone mass and preventing hip fractures. The researchers will follow this cohort of women for another five years.

Although selenium has protective effects against cancer in a variety of experimental systems, it is not clear if this protection is a result of selenoproteins (proteins that include a selenocysteine residue) or if low molecular weight selenocompounds are responsible for this activity. However, a recent study provides the first evidence that both selenoproteins and low molecular weight selenocompounds have a role in colon cancer protection.

A large prospective cohort study of Singapore Chinese men and women found an overall increased risk of developing colorectal

cancer in patients with diabetes. The researchers note that the diabetes and cancer risk link was not tied to obesity.

The NCI and others are identifying and characterizing a variety of genes and mutations associated with the development of colorectal cancer. Findings suggest a tumorigenic role of mutations in genes for serine kinases, threonine kinases, and COX-2, and an increased risk for sporadic colon cancer by inactivation of the gene, MGMT, by DNA methylation. A newly developed risk model provides clinicians with a tool to estimate the likelihood of individual patients carrying mutations in the MLH1 and MSH2 genes, the primary causes of HNPCC. Compared with the widely used Bethesda Guidelines, the new model would lead to the testing of fewer individuals but would miss fewer mutation carriers.

Five hundred pairs of siblings who have had colon or rectal cancer and precancerous polyps were recruited for the CGN-sponsored Sibling Pair Colon Cancer Study for identification of genetic and environmental factors involved in colorectal cancer development. The investigations are being conducted in individuals where there is no known HNPCC or familial adenomatous polyposis (FAP) in the hope of identifying cancer genetic susceptibility regions. Data are currently being analyzed. Additional information on this study is available online at http://biostatistics.mgh.harvard.edu/siblingpair.

The Colon 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 colon cancer. Information about this registry is available online at http://epi.grants.cancer.gov/CFR/about_colon.html.

Prevention

The NCI and other organizations are investigating the protective effect of NSAIDS on colorectal polyps and tumors. Researchers from the Adenoma Prevention with Celecoxib (APC) trial and another trial funded by Pfizer reported in April 2006 that daily use of the NSAID, celecoxib, significantly reduced the risk of precancerous polyps of the colon or rectum. The NCI halted the APC trial in late 2004 after data analysis showed a 2.5-fold increased risk of major fatal and non-fatal cardiovascular events for participants taking the drug when compared with those taking a placebo. In related research, results from the Polyp Prevention Trial suggest that individuals who are carriers of a particular genetic variant (IL-10 −1082 G>A) may not benefit from the chemoprotective effect of NSAIDs on adenoma polyp recurrence.

A large study has shown that people who took cholesterol lowering statins, the most frequently prescribed medication in the U.S., for at least five years had a decreased risk of developing colorectal cancer. The NCI is sponsoring a controlled, randomized clinical trial to rigorously test the efficacy of statins for prevention of colorectal cancer.

Researchers reported that HPV infection was found in more than half of 55 carefully examined tumor samples from patients with colorectal cancer and in none of 10 colorectal tissue samples from patients without cancer. However, further research is needed to establish a relationship between HPV infection and colorectal cancer. A vaccine for prevention of HPV infections responsible for 70 percent of cervical cancers has recently been approved by the FDA. (See previous Cervical Cancer Prevention section.)

Early Detection, Diagnosis, and Prognosis

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.

Researchers from the PLCO Cancer Screening Trial report that patient acceptance of flexible sigmoidoscopy examination was high. Although diagnostic followup varied according to polyp size, cancer or adenoma detection rates met expectations. However, in another study partly funded by the NCI, use of flexible sigmoidoscopy to screen women 50 years of age or older who are at average risk of colorectal cancer was found to miss nearly two-thirds

of advanced polyps. The investigators found that precancerous polyps in men tend to grow in the lower colon, but in women the polyps tend to grow deeper in the colon, which is beyond the range of this screening technology.

According to a study from the NCI and the CDC, many clinicians do not administer colorectal cancer screening with the in-home fecal occult blood tests (FOBT), as recommended in the U.S. Preventative Services Task Force's 2002 guidelines. Many surveyed clinicians use the in-office FOBT, which has not been proven to reduce colorectal cancer mortality. Furthermore, this and a second study report that many patients with positive FOBTs are not referred for colon exam. Other screening studies are comparing the immunochemical and traditional guaiac versions of the FOBT for accuracy in referring patients for colonoscopy.

Researchers report that improved colorectal cancer staging by lymphatic mapping may aid the selection of patients who are the best candidates for adjuvant chemotherapy. Lymphatic mapping entails injecting a dye at the primary tumor site just before surgical removal. The dye stains the sentinel lymph nodes, the first lymph nodes downstream from the tumor, which are removed and analyzed for metastatic tumor cells.

Researchers working with tumor samples from participants in a Phase III clinical trial have developed a gene expression profiles assay that predicts response of rectal carcinomas to neoadjuvant chemoradiotherapy. The implementation of gene expression profiles for treatment stratification and clinical management of cancer patients will require validation in large, independent studies.

Treatment

Avastin and cetuximab are monoclonal antibodies used in conjunction with chemotherapy to treat metastatic colorectal cancer. The NCI is supporting clinical trials to optimize the drug combinations used with these monoclonal antibodies. In 2006, the FDA approved another monoclonal antibody, panitumumab (Vectibix), an EGFR inhibitor, for the treatment of metastatic colorectal cancer that has progressed despite standard chemotherapy. Approval was based on clinical trials showing effectiveness in slowing tumor growth and, in some cases, reducing the size of the tumor.

A Phase I study has reported promising findings for a treatment vaccine that targets carcinoembryonic antigen (CEA), a protein associated with a variety of cancers, including colorectal cancer. Forty percent of patients in the trial, including some colorectal cancer patients, experienced stable disease when treated with the vaccine in conjunction with a compound known to enhance vaccine efficacy. Further clinical research is needed to determine survival outcomes with this form of therapy.

Survivorship

The results of two prospective, observational studies showed that patients with early to late stage colorectal cancer (with no distant metastases) who engaged in regular activity after diagnosis had a decreased likelihood of cancer recurrence and mortality of 40 to 50 percent or more when compared with patients who engaged in little or no activity. These findings held true regardless of levels of physical activity before cancer diagnosis or other risk factors for recurrence.

Health Disparities

Researchers report that colorectal cancer screening rates are rising for both men and women in the U.S., a trend that is driven by a sharp increase in the use of colonoscopy. However, less than half of those eligible undergo screening, and screening rates are higher in men than women. Furthermore, screening use remains lower for those of Hispanic ethnicity, at lower education levels, lacking health insurance, without a usual source of health care, and those who have not talked with a doctor in the past year.

According to a large prospective study, the use of adjuvant chemotherapy in patients with stage III colon cancer has increased significantly since recommendations from a 1990 NIH consensus conference advised clinicians to implement the practice. However, nearly one-third of patients received surgery only for treatment, particularly female and elderly patients. Another study found that 11 percent fewer black patients than white patients with colorectal cancer received adjuvant chemotherapy. Researchers analyzing Medicaid-linked SEER

data found that hospitalization due to side effects from the 5-fluorouracil family of drugs and low social or psychological support are the factors most closely related to whether patients with stage III colon cancer complete adjuvant chemotherapy. The authors suggest testing whether interventions to improve social and physical support for patients during treatment would improve adherence. Yet another study concluded that non-English-speaking patients with colorectal cancer were less satisfied with their care than English-speaking patients.

The NCI CRCHD is administering development of an innovative Patient Navigator Research Program, focusing on four cancers for which screening tests are available: breast, cervical, prostate, and colorectal. (See Cancer Control, Survivorship, and Outcomes research in the Breast Cancer section of this report.) Additional information on this program is also available online at http://crchd.cancer.gov/pnp/pnrp-index.html.

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. Based on the CDC estimates, the number of HIV/AIDS cases decreased 17 percent among females between 2001 and 2005. In 2005, the estimated rate of HIV/AIDS cases was 20.2 per 100,000 and about 26 percent of these were in females. There were about 14.9 per 100,000 cases of AIDS, 27 percent of which were in females. About 80 percent of HIV/AIDS transmission among women in 2005 occurred by high-risk heterosexual activity. While the numbers of deaths per year in the U.S. due to AIDS has decreased in the era of highly active antiretroviral therapy (HAART), the number of persons living with the disease has increased. Approximately 476,095 persons are currently living with HIV infection or AIDS in the 33 states with confidential name-based reporting. Of those, 27 percent were adult and adolescent women. Minorities accounted for 79 percent of cases in women, including 64 percent black females and 15 percent Hispanic women.

The longer life expectancy of HIV positive people on HAART, who are living with partially restored immune function, may increase the cumulative risk of developing both AIDS-defining and non-defining cancers.

The AIDS-defining malignancies are non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, and Kaposi's sarcoma (KS). The 23-fold increased risk of NHL is particularly concerning since this cancer ranks sixth in overall female cancer incidence and mortality. Although HIV-infected women who have initiated HAART experience significant reductions in overall cancer risks, NHL incidence remains higher in this population compared with the HIV-uninfected U.S. population. KS, although a rare cancer, is 200 times more likely to occur in HIV-infected women than in uninfected women. Some studies have found the risk of cervical neoplasia to be 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 both HIV and HPV have a 6.8-fold greater risk of invasive anal cancer than HIV-negative, HPV-positive women. And HIV-infected women have been found to have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

The NCI lymphoma SPORE located at the Johns Hopkins University 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. Additional information on this SPORE is available at http://spores.nci.nih.gov/current/lymphoma/lymphoma_docs/lymambinder.html.

NCI's AIDS Malignancy Program (AMP) provides coordination and programmatic support of AIDS-associated malignancy research across the NIH to provide opportunities for integrated, multidisciplinary investigations. Additional information on the AMP is available online at http://ctep.cancer.gov/resources/aidsmalignancy/.

The trans-NIH Centers for AIDS Research (CFAR) program provides administrative and shared research support to synergistically enhance and coordinate high-quality AIDS

research projects, both nationally and internationally. Core facilities provide expertise, resources, and services not readily obtained through more traditional funding mechanisms. Researchers at 20 CFARs study the natural history and pathobiology of HIV-related malignancies in diverse populations of men, women, and children, and they investigate the role of sex and gender in AIDS therapy and prevention through collaborative studies in women and girls. Additional information on the CFAR is available online at http://www.niaid.nih.gov/research/cfar.

Risk Factors

Since 1995, the NCI has co-funded the Women's Interagency HIV Study (WIHS) with the NIAID, the NICHD, and the NIDA. This effort supports the largest U.S. study of HIV infection in women that includes malignancy studies. A recent WIHS study estimated the risk of and risk factors for progression in HIV-infected women with abnormal cervical cytology but negative colposcopy. They found that the risk of progression is higher in HIV-infected women, but the absolute risk is low and becomes non-significant after controlling for HPV risk type, ethnicity, and colposcopic findings. More information on the WIHS is available at http://statepiaps.jhsph.edu/wihs.

Another WIHS study showed that, in HIV-positive women, the combination of increasing plasma HIV RNA level and decreasing CD4 cell count may be associated with HPV reactivation in sexually inactive women. The more moderate association between HIV coinfection and HPV persistence could partly explain why cervical cancer rates have not reached more epidemic proportions in HIV-positive women.

The Viral Epidemiology Branch (VEB) conducts multidisciplinary studies of carefully selected domestic and foreign populations with the goal of clarifying the relationship of infectious agents, especially viruses, to human cancer and other conditions. Investigators have reported a reduced risk of breast and postmenopausal endometrial cancer among women with AIDS. These findings are being followed up in studies to clarify the relationship of retrovirus infection and immunity to breast cancer.

A CFAR study is looking at risk factors for anal disease in HIV-infected women. Preliminary data suggest that anal HPV infection exceeds cervical HPV infection in this population.

The AMP-supported AIDS and Cancer Specimen Resource (ACSR) catalyzes epidemiological and pathogenesis studies of genetic and environmental risks for development of AIDS-associated cancer by enhancing collection, storage, and effective utilization of specimens from WIHS participants. The ACSR provides access to more than 140,000 specimens and associated clinical data collected from cohort studies, clinical trials, and other research. Additional information on the ACSR is available online at http://acsr.ucsf.edu.

Prevention

The 2006 *International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies* (ICMAIO) was sponsored by the AMP, the NCI's Office of International Affairs, the NCI Office of Women's Health, and the DHHS Office on Women's Health. Conference presentations highlighted HPV pathogenesis, molecular epidemiology of HPV subtypes associated with HIV in developing countries, and the potential impact of the newly approved HPV vaccine and other preventive strategies in reducing the risk of HPV-associated cancers in HIV-infected women.

Early Detection, Diagnosis, and Prognosis

WIHS researchers recently assessed the incidence of squamous intraepithelial lesions (SILs) in HIV-seropositive women with normal cytology results. Their findings suggest that the recommended cervical screening interval of three years in healthy women aged 30 years or older who have normal cytology results and a negative oncogenic HPV test may also be appropriate for HIV-infected women. However, the investigators note the need for a clinical trial to evaluate this strategy.

Treatment

NCI researchers are searching for more effective AIDS therapies that will reduce the incidence of AIDS-related malignancies and for treatments that will improve survival of patients with these malignancies. The NCI-funded AIDS Malignancy Consortium (AMC) conducts clinical treatment trials in HIV-associ-

ated malignancies. Ongoing trials include the investigation of combined modality therapy plus Erbitux in HIV-associated anal carcinoma, valproic acid in patients with KS, Gleevec in patients with KS, and a high-dose, short-course chemotherapy regimen for HIV-associated Burkitt's and Burkitt's-like lymphoma. The AMC is also developing studies to assess the safety and efficacy of HPV vaccines in women infected with HIV.

NCI's intramural HIV and AIDS Malignancy Branch (HAMB) conducts translational research on HIV infection and AIDS-related malignancies to develop novel therapies for AIDS and AIDS-related malignancies and to understand the effects of these therapies on disease pathogenesis. HAMB investigators were responsible for the early development of darunavir, an HIV protease inhibitor that was recently approved by the FDA as an anti-HIV therapy. Now, results from an early HAMB clinical trial show a promising effect of interleukin-12 (IL-12), which can act as both an immunostimulator and an antiangiogenesis agent, for treatment of patients with AIDS-related KS. Additional information on the HAMB is available online at http://ccr.cancer.gov/labs/lab.asp?labid=63.

Investigators have shown that treating South African women with a single dose of the drug, nevirapine (sdNVP), which is used to prevent mother-to-child transmission, induced mutations conferring resistance to this drug in approximately 70 percent of the study participants. These findings highlight the need for studies assessing the impact of sdNVP on the efficacy of subsequent antiretroviral therapy containing nevirapine or similar agents.

Training

The NCI is a co-sponsor of the AIDS International Training and Research Program (AITRP), which supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries. Additional information on the AITRP is available online at http://www.fic.nih.gov/programs/aitrp/aitrp.html.

Initiatives

Request for Applications (RFAs)

- **International Tobacco and Health Research and Capacity Building Program**
  This RFA, which was issued by the FIC and the NCI, solicits research to address the burden of tobacco consumption in low- and middle-income nations by (1) pursuing observational, intervention, and policy research of local relevance; and (2) building capacity in these regions in epidemiological and behavioral research, prevention, treatment, communications, health services, and policy research. (RFA-TW-06-006)
- **Nutritional Modulation of Genetic Pathways Leading to Cancer**
  The NCI funds four research centers as part of the Nutritional Modulation of Genetic Pathways Leading to Cancer U54 Cooperative Agreement. The goal of this initiative is to expand and facilitate fundamental research that will define the molecular basis by which dietary components influence cancer prevention. (RFA-CA-03-00)
- **Comprehensive Minority Institution/Cancer Center Partnership (P20)**
  The NCI invited applications for partnerships and feasibility studies between minority-serving institutions and NCI-designated Cancer Centers (or groups of Centers) to develop a stronger national cancer program aimed at understanding the reasons behind the significant cancer disparities and impact on minority populations. (RFA-CA-06-011)
- **Tumor Microenvironment Network (TMEN) (U54)**
  This RFA supports the NCI TMEN, which consists of interconnected, multidisciplinary teams of investigators and collaborative groups that will delineate mechanisms of tumor-stroma interactions in human cancer. Up to six research programs will be supported, each consisting of multidisciplinary teams with expertise in specific tumor site(s) and using human cancer samples and/or well-defined vertebrate models. (RFA-CA-06-014)

- **Exploratory Grants for Increasing the Utilization and Impact of the National Cancer Institute's Cancer Information Service (R21)**
  The purpose of this RFA is to promote research to develop and test national, regional, or community-based interventions that increase the use and assess the impact of scientifically accurate and up-to-date cancer information delivered through existing CIS resources. (RFA-CA-06-015)
- **Cancer Research Network (U19)**
  The goal of this RFA is to increase scientific knowledge in cancer epidemiology, risk factors, prevention, early detection, diagnosis, prognosis, treatment, and end-of-life care in the context of community-based health care delivery. (RFA-CA-06-505)
- **Innovative Technologies for Molecular Analysis of Cancer**
  The NCI invites applications using different mechanisms to develop cancer-relevant molecular analysis technologies, including detection of alterations of genomic DNA; measurement of gene expressions and products; analysis and detection of gene and/or cellular products; identification and characterization of exogenous infectious agents in cancer; and assaying the function of signal transduction networks involved in cancer. (RFA-CA-07-001, RFA-CA-07-006, RFA-CA-07-007, RFA-CA-07-015, RFA-CA-07-016)
- **Small Animal Imaging Resource Program**
  These programs support: (1) imaging technologies for small animals that provide information related to malignancy in vivo; (2) new imaging technologies appropriate for small animals; (3) the development of probes for the imaging technologies provided; (4) small animal anesthesia and care; and (5) training for professional and technical personnel in cancer-related small animal imaging. (RFA-CA-07-004)
- **Advanced Proteomic Platforms and Computational Sciences for the NCI Clinical Proteomic Technologies Initiative**
  The NCI invites applications in proteomic technology to be applied to the measurement of proteins and peptides of interest in clinical cancer studies and supports two focus areas: (1) the development of technology for protein and peptide detection, recognition, measurement, and characterization in biological fluids, and (2) computational, statistical, and mathematical approaches for the analysis, processing, and exchange of large proteomic data sets. (RFA-CA-07-005)
- **Cancer Genome Characterization Centers**
  This RFA is designed to establish a collaborative group of multidisciplinary Cancer Genome Characterization Centers (CGCCs) as part of The Cancer Genome Atlas (TCGA) Pilot Project. The Centers will use genomic and/or epigenomic analysis technologies to pioneer the systematic, high-resolution, comprehensive characterization of cancer-related genomic alterations. (RFA-CA-07-014)
- **Development of Advanced Genomic Characterization Technologies**
  These RFAs, which were issued by the NCI and the NHGRI for research using different NIH mechanisms, are a part of the Cancer Genome Atlas Pilot Project and solicit research projects to develop highly innovative and novel genomic analysis technologies to provide new insights and understanding into the role of genetic alterations in cancer. (RFA-CA-07-021, RFA-CA-07-029, RFA-CA-07-030)
- **Application of Emerging Technologies for Cancer Research**
  The NCI invites projects using different NIH mechanisms to evaluate the usefulness of emerging molecular technologies that are ready for initial application to clinical or biological questions in cancer research. Projects should demonstrate that the technology is robust and yields reproducible measurements. (RFA-CA-07-002, RFA-CA-07-009, RFA-CA-07-017, RFA-CA-07-018, RFA-CA-07-019)
- **Community Clinical Oncology Program (CCOP)**
  The CCOP network is designed to increase the involvement of community oncologists and their patients in NCI-sponsored clinical trials; involve a wider segment of the community in cancer clinical trials, including minorities, women, and other underserved populations; and accelerate the transfer of knowledge gained from clini-

cal trials to community oncology practices. (RFA-CA-07-025)

- **Minority-based Community Clinical Oncology Program**
  The objective of this initiative is to bring cancer clinical trials to minority individuals in their own communities and to involve physicians in these communities in NCI-approved clinical trials in an effort to reduce health disparities in minority populations. (RFA-CA-07-026)

Selected Program Announcements (PAs)

- **Stem Cells and Cancer**
  These PAs, which were issued by the NCI and the NIA, are intended to promote research on all aspects of tumor stem cell biology and on the genes and proteins responsible for the tumor stem cell phenotype. Studies on the characterization of tumor stem cells from the broad spectrum of solid and liquid tumors not already examined, markers potentially shared by tumor stem cells and normal stem cells, and the biochemical and molecular regulation of normal and tumor stem cell function are encouraged. (PA-05-086, PA-06-282)
- **Diet-induced Changes in Inflammation as Determinants of Colon Cancer**
  The goal of this PA is to foster research that will identify and characterize diet-induced changes in inflammation linked with colon cancer risks. The focus should be on defining the physiological significance of diet in modulating inflammatory processes that may be linked to colon cancer development. (PA-05-125)
- **Image-guided Cancer Interventions**
  These PAs support the development and clinical validation of systems for Image-Guided Interventions (IGIs) for cancer through the STTR and SBIR programs. The research will foster: the development and optimization of fully integrated cancer imaging, monitoring, and therapy systems; validation through clinical evaluations; development of multiple prototype for multisite clinical evaluations; and partnerships among small businesses, large businesses, and academic clinical centers, to reach the research goals. (PA-06-031, PA-06-032)
- *In Utero* **Exposure to Bioactive Food Components and Mammary Cancer Risk**
  The PA, which was issued by the NCI, the NIEHS, and the NIH Office of Dietary Supplements (ODS), supports applications on *in utero* exposures that are determinants of some cancers occurring in children and young adults. Studies that apply new high-throughput genomic, epigenomic, proteomic, and metabolomic technologies or genetically engineered animal models to determine how dietary and/or environmental chemical exposures *in utero* influence adult breast cancer susceptibility are encouraged. (PA-06-277)
- **Understanding the Effects of Emerging Cellular, Molecular, and Genomic (CMG) Technologies on Cancer Health Care Delivery**
  These PAs support health services research on the use of CMG technologies in cancer care related to quality of care; organizational barriers and change factors in use; cost and cost-effectiveness; disparities in access and efficacy; monitoring of cross-sectional patterns of care and time trends; impact on existing standards of care; and influence on cancer outcomes, such as incidence, progression, mortality, survival, and quality of life. (PA-06-280, PA-06-281)
- **Immunoregulation of Gastrointestinal Carcinogenesis**
  These PAs focus on the role of the mucosal immune system in initiating and maintaining inflammatory responses leading to the development of premalignant and malignant gastrointestinal cancers. Research efforts should lead to an understanding of how immune responses participate in gastrointestinal carcinogenesis. (PA-06-289, PA-06-290)
- **Protein Biomarkers of Infection-associated Cancers**
  This PA, which was issued by the NCI and the NIDCR, encourages the identification of proteomic markers for risk assessment and early detection in individuals exposed to infectious agents that have been linked to cancer. Agents of interest include HPV, hepatitis B and C viruses, EBV, and Simian

Virus 40. Projects on early cervical, lung, and colon cancers among HIV patients, and bacterial etiology in cancer are encouraged. (PA-06-297)

- **Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis**
  The objective of this PA is to promote the evaluation of new molecular or cellular characteristics of premalignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. Translational studies that identify promising new means for cancer detection and diagnosis and determine whether potential clinical utility justifies further investment are encouraged. (PA-06-299)
- **Studies of the Economics of Cancer Prevention, Screening, and Care**
  This PA, which was issued by the NCI and the AHRQ, invites applications for research directed at increasing the knowledge base in the area of the economic aspects of cancer prevention, screening, and care to promote the optimal design of cancer prevention and control trial studies and interventions and to facilitate the formulation of effective health care policy related to cancer prevention and control. (PA-06-304)
- **Decisionmaking in Cancer: Single-event Decisions**
  This PA invites applications for research projects that will enhance understanding of human decisionmaking processes so that individuals can make more informed and satisfying choices regarding their health as it relates to cancer prevention, detection, treatment, survivorship, or end-of-life care. (PA-06-305)
- **The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery**
  These PAs were issued by the NCI, NIDDK, OBSSR, NHLBI, NIBIB, and NIDA. The purposes of these PAs are to: (1) to improve the measurement of racial/ethnic discrimination in health care delivery systems; (2) enhance understanding of the influence of racial/ethnic discrimination in health care delivery; and (3) reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination on health care delivery systems in the U.S. (PA-06-306, PA-06-348)
- **Decisionmaking in Health: Behavior Maintenance**
  The purpose of this PA, which was issued by the NCI, NIDA, and NIAAA, is to expand our knowledge of basic decisionmaking processes underlying the initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases. (PA-06-337)
- **Research on Malignancies in AIDS and Acquired Immune Suppression**
  The goal of this PA, which was issued by the NCI and the NIDCR, is to encourage applications ranging in scope from basic science through molecular epidemiology to preclinical studies and including but not limited to: (1) developing and using animal and cell culture models to study disease pathogenesis; (2) discovering and characterizing new viral and microbiological agents that act as co-factors in tumor promotion or progression; (3) developing and using predictive models for the preclinical evaluation of new therapies against AIDS-related malignancies; (4) developing preclinical applications to translate basic knowledge of AIDS-related malignancies toward the development of new treatments; (5) defining the molecular epidemiology of HIV-associated cancers and their preneoplastic conditions; and (6) discovering, developing, and using biomarkers of cancer risk, progression, or response to treatment. (PA-06-338)
- **Memory T Lymphocytes in Cancer Immunology**
  These PAs are intended to focus research on memory T lymphocytes and the cells and molecules with which they interact. The overarching objective is to ultimately improve the prospects for the development and application of vaccines and immunotherapies that can be used to successfully prevent and treat cancers in humans. (PA-06-349, PA-06-350)

- **Exfoliated Cells, Bioactive Food Components, and Cancer**
  This PA promotes innovative preclinical and clinical research to evaluate the utility of using exfoliated cells to monitor variation in dietary intakes of bioactive food components thought to be involved with cancer prevention. Potential areas of investigation include studying the effect of individual dietary components on molecular or biochemical processes and predicting the anticancer responses in surrogate samples, blood, and its constituents and target tissues. (PA-06-359, PA-06-360)
- **Testing Tobacco Products Promoted to Reduce Harm**
  This PA, which was issued by the NCI and NIDA, encourages multidisciplinary research on the chemical composition, use, exposure to toxic agents, addictive properties, differential toxicity, and individual and public health impact of potential reduced-exposure tobacco products. (PA-06-361)
- **Cancer Surveillance Using Health Claims-based Data**
  The NCI, in partnership with the AHRQ, supports research directed at the use of health claims data for cancer surveillance, including studies of cancer detection, treatment, and/or outcomes. (PA-06-385, PA-06-386)
- **Novel Technologies for *In Vivo* Imaging**
  These PAs invite applications for the development and delivery of novel image acquisition or enhancement technologies and methods for biomedical imaging and image-guided interventions and therapy. (PA-06-398, PA-06-399)
- **Developmental Projects in Complementary Approaches to Cancer Care**
  The intent of this PA, which was issued by the NCI, NINR, and NCCAM, is to encourage the development of basic and clinical (prevention, therapeutic, and palliative) cancer research in complementary approaches and to facilitate communication and collaboration between practitioners in complementary approaches and the conventional cancer research communities. (PA-06-400)
- **Studies of Energy Balance and Cancer in Humans**
  The NCI invites applications that focus on factors affecting energy balance and mechanisms influencing cancer risk, prognosis, and quality of life. Projects may include new analyses of existing datasets to additional collection of data and biological specimens in ongoing investigations. (PA-06-404, PA-060405)
- **Diet, Epigenetic Events, and Cancer Prevention**
  These PAs, which were issued by the NCI, NIAAA, NIDDK, and ODS, are intended to promote preclinical and clinical research to determine how diet, dietary factors, and dietary supplements impact epigenetic processes involved in cancer prevention. Research supported by this initiative could address how bioactive food components regulate epigenetic events for cancer prevention, how bioactive food components might alter aberrant epigenetic patterns or events and restore gene function, and how these components might circumvent or compensate for genes and pathways that are altered by epigenetic events. (PA-06-412, PA-06-413, PA-06-414)
- **Exploratory/Developmental Grant for Clinical Studies of Complementary and Alternative Medicine**
  The NCI and the NCAM invite high-quality exploratory/developmental clinical research grant applications that focus on CAM approaches related to cancer symptoms and side effects of cancer treatment as well as survivorship. It is anticipated that these pilot studies will generate supporting preliminary clinical data that can be used to support larger clinical studies. (PA-06-510)
- **Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis**
  The purpose of this PA to encourage clinicians, epidemiologists, geneticists, statisticians, and translational cancer control and prevention researchers to improve existing models for cancer risk, prognosis, or response to therapy by developing innovative research projects that: use existing data; develop new models for cancer risk and prognosis; and validate new models and

evaluate their utility in research and clinic settings. (PA-07-022, PA-07-021)

- **Research on Malignancies in AIDS and Acquired Immune Suppression**
  The goal of this PA, which was issued by the NCI and the NIDCR, is to encourage applications ranging in scope from basic science through molecular epidemiology to preclinical studies and including but not limited to: (1) developing and using animal and cell culture models to study disease pathogenesis; (2) discovering and characterizing new viral and microbiological agents that act as co-factors in tumor promotion or progression; (3) developing and using predictive models for the preclinical evaluation of new therapies against AIDS-related malignancies; (4) developing preclinical applications to translate basic knowledge of AIDS-related malignancies toward the development of new treatments; (5) defining the molecular epidemiology of HIV-associated cancers and their preneoplastic conditions; and (6) discovering, developing, and using biomarkers of cancer risk, progression, or response to treatment. (PA-07-173)
- **Specialized Programs of Research Excellence (SPOREs) in Human Cancer for Year 2005-2006**
  SPOREs conduct translational research in the prevention, etiology, screening, diagnosis, and treatment of organ-specific cancers. Each SPORE is expected to conduct research that will have immediate impact on reducing incidence and mortality of human cancer and must include a minimum of four translational research projects, cores, developmental research, and career development programs. (PAR-05-042)
- **Quick-Trials for Novel Cancer Therapies: Exploratory Grants**
  This PA will continue to support scientific, technological, clinical, and logistical needs in novel cancer therapy development. (PAR-06-451)
- **The Role of Nuclear Receptors in Tissue and Organismal Aging**
  These PAs, which were issued by the NCI, NIA, NIDDK, and NIEHS, support projects aimed at understanding the role of nuclear hormones and their regulation in a number of human malignancies (e.g., thyroid, lung, colon, endometrium, ovary, and breast) and includes research on the role of the coregulators in regulating transcription, influencing epithelial-stromal interactions during cancer progression contributing to hormone resistance, as well as in determining therapeutic response. (PAS-06-466, PAS-06-467)

Conferences and Workshops

- **The 10th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies**
  Convened in Bethesda, MD on October 16-17, 2006
- **Cancer Survivorship: Embracing the Future**
  Convened in Bethesda, MD on October 4-6, 2006
- **Intraperitoneal Chemotherapy for Ovarian Cancer Symposium at the International Conference on Cancer Nursing**
  Convened in Toronto, Canada on September 27 - October 1, 2006
- **Consensus Guidelines for Management of Women with Cervical Abnormalities**
  Convened in Bethesda, MD on September 17-19, 2006
- **Personalized Breast Cancer Therapy Symposium at the 25th Congress of The International Association of Breast Cancer Research (IABCR) Conference**
  Convened in Montreal Canada on September 15-18, 2006
- **Second Biennial Workshop to Increase Diversity in Research Funding**
  Convened in Palm Desert, CA on September 6-8, 2006
- **Team Up: Cancer Screening Saves Lives 2006 National Meeting**
  Convened in Charleston, SC on August 1-4, 2006
- **Health Disparities Research Methods Training Symposium in conjunction with the IUCC World Conference and the 13th World Conference on Tobacco OR Health**
  Convened in Washington, DC on July 12, 2006

- **NCI Advocacy Summit on Listening and Learning Together: Building a Bridge of Trust**
  Convened in Bethesda, MD on June 19-20, 2006
- **NIH State-of-the-Science Conference on Tobacco Use: Prevention, Cessation, and Control**
  Convened in Bethesda, MD on June 12-14, 2006
- **3rd Annual Uterine Cancer Biology Symposium**
  Convened in St. Louis, MO on May 13, 2006
- **NCI Symposium on State-of-the-Science Health Communication**
  Convened in Bethesda, MD on May 10, 2006
- **Progesterone Receptor Modulators and the Endometrium: Changes and Consequences**
  Convened in Bethesda, MD on April 7-8, 2006
- **NCI Workshop to Assess the Evidence for a Randomized Clinical Trial on Weight Control and Prevention of Breast Cancer Recurrence**
  Convened in Rockville, MD on March 15-16, 2006
- **Enhancing Interactions To Reduce Cancer Health Disparities**
  Convened in Bethesda, MD on November 17-18, 2005
- **Ovarian Cancer: Prevention & Detection of the Disease & Its Recurrence**
  Convened in Pittsburgh, PA on October 24-25, 2005
- **9th International Conference on Malignancies in AIDS an other Immunodeficiencies**
  Convened in Bethesda, MD on September 26-27, 2005
- **Tobacco Control Policies: Do They Make a Difference for Low SES Women and Girls?**
  Convened in Bethesda, MD on September 22-23, 2005
- **Transplacental Exposure to Nucleoside Analogs: Mitochondrial Damage and Fetal Health Symposium at the 9th International Conference on Environmental Mutagens**
  Convened in San Francisco, CA on September 3-8, 2005
- **Breast Cancer, Prevention and Gynecologic Malignancies Combined Faculty Retreat on Prevention**
  Convened in Cumberland, MD on July 20-22, 2005
- **Diet and Communication: What Can Communication Science Tell Us About Promoting Optimal Dietary Behavior?**
  Convened in Bethesda, MD on July 14-15, 2005
- **4th International Conference on Cervical Cancer**
  Convened in Houston, TX on May 19-22, 2005
- **Helene Harris Memorial Trust 10th International Forum on Ovarian Cancer**
  Convened in Washington, DC on April 5-7, 2005
- **Workshop on Women and Cancer at the 2nd Clinical Health Psychology Institute on Women's Health**
  Convened in Washington, DC on April 1-2, 2005
- **4th Annual Intraductal Approach to Breast Cancer Symposium**
  Convened in Santa Barbara, CA on March 10-13, 2005

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 P.L.105-277, which was signed by the President in October 1998. The mission of the NCCAM is to explore complementary and alternative healing practices in the context of rigorous science, train CAM researchers, and 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 interventions proven to be safe and effective become accepted as mainstream health care practices. The NCCAM groups CAM practices within the following areas: (1) whole

medical systems (i.e., traditional Chinese medicine, naturopathic medicine, Ayurveda); (2) mind-body medicine (i.e., meditation, yoga); (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). The NCCAM conducts and supports basic and applied (clinical) research and research training within these areas.

The 2002 NHIS 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, the most prevalent CAM practice, was excluded from the definition of CAM, more than a third (36 percent) still reported use of CAM in the previous 12 months. 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 (CVD). CAM therapies for women treat a variety of conditions, such as menopausal symptoms, breast cancer, osteoporosis, pain associated with osteoarthritis and fibromyalgia, and reproductive issues. Thus, NCCAM's research portfolio includes investigations focused on a variety of diseases, using a myriad of CAM therapeutic interventions. During FY 2005 and 2006, NCCAM's Senior Advisor for Women's Health served as a coordinator for women's health activities and a liaison to the NIH ORWH.

Accomplishments

Menopause

In 2002, the Women's Health Initiative (WHI) found increased risk for CVD, 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 U.S. 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 WHI, some industry 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 that are currently commonly used for menopausal symptoms, including botanicals or herbs (i.e., black cohosh, dong quai, and ginseng), paced respiration, meditation, magnet therapy, acupuncture, and homeopathy. The efficacy and safety of many of these therapies have not yet been definitely determined. 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, safe and effective alternatives to hormone-based therapies are needed for women with a history of breast cancer whose tumors may be hormone dependent.

Over the past several years, the NCCAM has developed a multipronged approach to improving our knowledge of CAM for the treatment of menopausal symptoms. One area of specific interest has been to better understand the quality of measures of hot flashes because the studies testing the efficacy of treatments for menopausal symptoms depend on the quality of these outcome measures. In response to an RFA issued in FY 2005, the NCCAM awarded several Phase I SBIR grants to small businesses to develop tools and technology to improve the measurement of sternal skin conductance. In response to an RFA in FY 2006, additional grants were awarded to the most successful of these small businesses to continue to facilitate development and validation of high-quality and noninvasive instruments that will enable the collection of long-term data on menopausal symptoms under ambulatory conditions. These awards followed the state-of-the-science conference

on the management of menopause-related symptoms in March 2005 that the NIA jointly sponsored with the NCCAM, the ORWH, and others. This meeting assessed a range of therapies to treat menopausal symptoms, including CAM modalities, and recommended that the NIH mount an interdisciplinary effort to identify the causes of and to develop effective and safe treatments for vasomotor symptoms, vaginal atrophy, and sleep disturbances. Since that SOS conference, two workshops have been convened to continue to identify the research opportunities for interventions targeting menopausal symptoms.

One botanical supplement in common use by women for the treatment and relief of menopausal symptoms is black cohosh. Although there is a growing literature studying the efficacy of black cohosh for menopausal symptoms, the results are inconsistent. In addition, several case reports of hepatotoxicity, a question regarding potential estrogenic activity of black cohosh, and putative effects of that activity on breast and prostate tissue have highlighted the need to review evidence regarding the safety of black cohosh. The jointly sponsored workshop by the NCCAM and the NIH ODS that was held in 2004 to discuss issues of safety with black cohosh concluded that the importance of patient safety mandates that liver function should be carefully monitored in all clinical studies of black cohosh. New developments since that time suggest that black cohosh does not increase breast cancer risk, may inhibit breast cancer cell growth, and may serve a protective effect. As a followup, the ODS and the Center for Food Safety and Applied Nutrition (CFSAN) at the FDA, with input from the NCCAM, are planning another workshop to continue to monitor recent developments regarding the safety of black cohosh.

In addition to the workshops and conferences cited above, the NCCAM supports a range of research projects on menopause through individual project and center grants. Some of this research is aimed at providing much-needed information on the safety and efficacy of CAM therapies used for menopausal symptoms, while more basic research provides valuable information on active ingredients, mechanisms of action, dose-ranging information, and bioavailability data. The NCCAM has invested in both clinical studies and basic science studies in this area. A recent finding from a study co-funded by the NCCAM and the NIA studied the efficacy of black cohosh in reducing hot flashes and night sweats among peri- and postmenopausal women. Approximately 350 women, all of whom who reported two or more vasomotor symptoms, such as hot flashes and/or night sweats, daily at the beginning of the study, participated in the Herbal Alternatives (HALT) for Menopause Study. This randomized, double-blind trial compared several botanical supplements with both conventional estrogen therapy and placebo. Results indicated that neither black cohosh alone or in conjunction with other botanical products resulted in fewer vasomotor symptoms relative to placebo. This is in contrast to the effects of estrogen, which was associated with clinically significant reductions in hot flashes and night sweats when compared with the placebo. This well-designed study underscores the importance of undertaking rigorous investigations to study the potential efficacy of CAM practices for the relief of menopausal symptoms.

Additional and ongoing clinical research on menopause targets several other CAM botanical therapies in addition to black cohosh, including red clover, soy and other phytoestrogens, as well as the use of non-botanical treatments (e.g., therapeutic touch, meditation) to assist women in coping with a range of menopausal symptoms, such as hot flashes, osteoporosis, and cognitive and affective problems. Examples of more clinically oriented research include several investigations funded with support from the ORWH and the ODS. For example, the NCCAM is supporting a study on the impact of phytoestrogens on cognition, affect, and atherosclerosis, and a randomized, controlled trial investigating the effects black cohosh and red clover, compared to conventional hormone therapy, on neuropsychological and neuroimaging outcomes among menopausal women. These two studies will be instrumental in identifying the utility of promising botanical products for the treatment of menopausal symptoms. Other investigations of promising nonbotanical therapies include a study testing the efficacy of meditation for menopausal symptoms among perimenopausal women and a separate study of meditation among breast cancer survivors.

The Center on Botanical Dietary Supplements for Women's Health in Chicago, supported by the ODS, the NCCAM, and the ORWH, 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, including a Phase II study of black cohosh 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, CVD, 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 endometrial markers.

Reproductive Issues

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 has funded a basic research project to look at the molecular mechanisms of Vitex agnus-castus L. (VAC or chasteberry) in PMS. This study is evaluating the affinity of different VAC extracts for opiate receptors, as well as binding and activation of brain opiate receptors, in a murine model. To date, the investigators have demonstrated that VAC can act as an agonist at the mu-opioid receptor, which supports its beneficial actions in PMS.

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; thus, the treatment options for adolescents with endometriosis are limited.

The NCCAM is funding a developmental center at the New England School of Acupuncture that is investigating the effects of acupuncture on chronic pelvic pain in adolescent and young women with endometriosis. The results of this study will be available soon.

Another issue related to reproduction is contraception. The herbal product, St. John's wort, has been shown to affect the metabolism of many drugs by induction of cytochrome P-450. An NCCAM-funded randomized, blinded, clinical trial is examining the effects of chronic use of St. John's wort on metabolism of levonorgestrel and its implications for contraceptive efficacy.

Another basic science study, co-funded by the ORWH, focuses on lactocin 160, a bacteriocin produced by Lactobacillus rhamnosus strain 160 that is found in healthy vaginas. Bacterial vaginosis (BV) results when healthy vaginal lactobacilli are replaced by pathogenic microflora. The proposed experiments will characterize the antimicrobial activity of lactocin 160 and the resistance of healthy vaginal microflora. Importantly, the mechanism of action of lactocin 160 will be determined and its activity optimized. Given that current treatment of BV (metronidazole and clindamycin) is associated with both toxicity to healthy microbes and a high rate of BV recurrence, these studies have great potential to result in a natural antimicrobial peptide that protects the lower genital tract from colonization by undesired pathogenic flora without inhibition of beneficial lactobacilli growth. A natural-based, low toxicity, inexpensive, female health product would be beneficial for the health of women (and in pregnancy, for the fetus), especially in disadvantaged communities.

Polycystic ovary syndrome (PCOS) is the most common endocrine-related disorder among women of childbearing age and the most common reason for anovulatory infertility. Six percent of women develop PCOS. The disorder is characterized by insulin resistance,

and up to 20 percent of patients develop impaired glucose tolerance or diabetes at an early age. Conventional treatment of PCOS focuses on hormonal suppression of sex steroid production, but one significant side effect is frequently an elevation of plasma glucose and increased insulin resistance. Thus, effective CAM treatments for the condition could be significant. The NCCAM is funding several investigations of CAM interventions for the treatment of PCOS that, if effective, may result in fewer side effects. One such study is testing the efficacy of acupuncture for increasing ovulatory frequency, normalizing the FSH/LH ratio, and normalizing FSH and LH mean concentrations among women diagnosed with PCOS. In addition, the NCCAM is supporting a study to test the effects of polyunsaturated fatty acid (PUFA)-rich walnuts on glucose homeostasis in women with PCOS.

Arthritis and Fibromyalgia

The prevalence of arthritis in the U.S. 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 an 18 percent increase in use in this population since 1990. 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 percent 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. NCCAM has supported 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 had sufficient statistical power to test for treatment effect differences by gender. Both studies have been completed, and their results published and summarized below.

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. One of the longest and largest randomized controlled Phase III clinical trials of acupuncture ever conducted was supported by the NCCAM and recently completed in 2005. There were 570 patients with osteoarthritis of the knee who 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 their primary care physicians, which included anti-inflammatory medications, non-steroidal anti-inflammatory drugs, and opioid pain relievers. The study demonstrated that individuals receiving acupuncture had greater pain relief and improved function than individuals receiving sham acupuncture or control, thus indicating that acupuncture is an effective complement to standard care.

The NCCAM and the NIAMS jointly awarded a contract to the University of Utah to conduct a randomized, controlled Phase III clinical trial of glucosamine and chondroitin sulfate for treatment of OA of the knee. There were 1,583 patients with OA randomized to receive daily 1,500 mg of glucosamine hydrochloride, 1,200 mg of chondroitin sulfate, both glucosamine and chondroitin sulfate, 200 mg of celecoxib, or placebo for 24 weeks. Subjects were allowed to take up to 4,000 mg of acetaminophen daily as a "rescue remedy." The clinical findings were that neither glucosamine, chondroitin sulfate nor their combinations were more effective than placebo for reducing knee pain. However, a subgroup of subjects with moderate-to-severe knee pain at baseline did have significantly reduced pain with the combination of glucosamine and chondroitin sulfate compared with placebo, whereas none of the other interventions, including celecoxib, was significantly different than placebo for this subgroup of subjects. Data analysis is ongoing

for the effects of the interventions on changes in knee joint space, as assessed by x-ray.

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. Scientists at the Arizona Center for Phytomedicine Research in Tucson studied Curcuma longa rhizome (powdered turmeric root), Zingiber officinale rhizome (powdered ginger root), and the gum resin of Boswellia serrata (boswellia). Findings indicate that boswellia does not ameliorate inflammation in a murine model and at higher doses produces hepatotoxic effects in mice. Analyses of ginger 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 derivatives 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 rheumatoid arthritis (RA) and prescription of herbal formulas for women. Another R21 grant that is co-funded by the ORWH is examining the modulation of autoimmunity by green tea polyphenols. Investigators from the University of Maryland will determine the effects of green tea polyphenols on the proliferative and cytokine response of T cells and whether green tea polyphenols are additive or synergistic with Bhsp65 carboxy-terminal determinant peptides for the prevention and/or treatment of adjuvant-induced arthritis. An additional 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, metabolic, 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.

Another CAM intervention for OA is external Qi gong therapy, which is a component of traditional Chinese medicine and is considered by the NCCAM to be in the energy medicine domain. The NCCAM has funded a pilot randomized trial of external Qi gong therapy for OA that is scheduled to be completed in FY 2007. Seventy percent of these subjects will be women.

The NCCAM has funded a Career Development Award for a rheumatologist who is studying the efficacy of prolotherapy for treatment of OA knee pain. Prolotherapy consists of injecting a "proliferants" solution into the ligaments of a joint or tendons of relevant muscles, which results in structural changes in these connective tissues and subsequently pain relief. Two-thirds of the subjects in this study are women.

CAM treatments are increasingly being used by patients with chronic pain and rheumatic diseases to help them cope with difficult symptoms and stress associated with their medical condition. While patients find these treatments helpful, there is limited scientific evidence for the efficacy of these interventions. It is undetermined whether these interventions have significant effects on disease activity or affect health outcomes in afflicted patients. The NCCAM has funded a study to compare a novel alternative behavioral intervention, Tai Chi Chih, a manualized, standard form of tai chi, with a commonly used behavioral intervention, relaxation therapy, on measures of clinical outcomes (disease activity, health functioning) in adults with RA. In addition, the study will explore the biobehavioral mechanisms (pro-inflammatory cytokines, affective response) through which Tai Chi Chih may contribute to improvements in the health of RA patients. Ninety percent of the subjects in this study will be women.

The RA symptoms of pain, fatigue, sleep disturbances, and depression often become worse for women during menopause. These symptoms frequently persist in spite of the use of non-steroidal anti-inflammatory drugs and disease modifying anti-rheumatic drugs. In two uncontrolled studies, persons with RA reported improvements in pain and joint swelling after using low strength pulse-electromagnetic fields

(PEMF). The NCCAM has funded a pilot study to investigate the magnitude of effects of low-strength PEMF on reducing the symptoms of pain, fatigue, sleep disturbances, and depression, as well as physiologic factors, in postmenopausal women with RA. The study will also test the feasibility of the proposed design. Participants will be randomly assigned to one of three treatment groups: active PEMF, sham PEMF, or standard care.

Fibromyalgia is a chronic, debilitating disorder that disproportionately affects women. Research demonstrating the therapeutic effectiveness of any single intervention targeting the multisymptomatic 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 Qi gong 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 overall health when compared with individuals receiving placebo. Additional work is underway 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. A recently completed efficacy study of a variant of EEG biofeedback called Low-Energy Neurofeedback System (LENS) for fibromyalgia found that LENS was no more effective than placebo for treatment of fibromyalgia symptoms.

Other Bone and Skeletal Diseases

Estimates of one-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 more than one million lost workdays per year. Direct and indirect costs for this condition are estimated at $50 billion a year in the U.S. 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 these conditions. The 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. A new study by Western States Chiropractic College is determining the optimal dose of spinal manipulation for treatment of subjects with chronic low back pain.

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. More than 50 percent of women who fracture a hip do not regain the level of functioning experienced prior to fracture. Several NCCAM-funded studies of menopausal women include bone density as an outcome measure in research using botanicals and phytoestrogens. The Center for Botanical Dietary Supplements Research in Women's Health is an NCCAM-supported center conducting studies on isoflavones and osteoporosis among middle-aged women. The NCCAM also supports researchers at the University of Connecticut through an Exploratory Program Grant for Frontier Medicine. This center is evaluating the effects of therapeutic touch and healing touch on bone metabolism and on fibroblast biology, and a clinical study is investigating the effect of therapeutic touch on bone metabolism in postmenopausal women with wrist fractures.

The NCCAM is funding a study of the efficacy of tai chi for osteopenic women. As part of aging in both men and women, bone mineral density (BMD) decreases, which increases the risk of fracture. During menopause, women's BMD decreases more rapidly that at other

times of life, making women at greater risk of fractures than men. Preliminary data indicates that tai chi may be efficacious for reducing the rate of BMD decrease.

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, a pilot/Phase II trial is evaluating traditional Chinese medicine and naturopathic medicine in comparison with usual care for women with temporomandibular disorders (TMD).

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 CAM modalities commonly used by cancer patients or survivors include supplements, such as beta carotene, melatonin, enzymes, hydrazine, coenzyme Q10, shark cartilage, massage, and mind-body approaches, such as yoga.

The NCCAM funded the Center for Cancer Complementary Medicine at the Johns Hopkins University as well as a Developmental Center that brings together the University of Minnesota with Bastyr University, a naturopathic medical school, to study the effects of a fungus (Trametes versicolor) on immune system function. This fungus is commonly used as a complement to conventional cancer therapies in Asian medicine systems. Other research projects are focused on other botanicals, acupuncture, energy therapies, such as polarity therapy, and massage. Some research is clinically focused, such as projects exploring the effects of different types of massage therapy on lymphedema associated with conventional cancer therapies and a project exploring the ability of massage to improve quality of life for terminal cancer patients.

Other NCCAM-funded 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 animal models. 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.

CAM is used at all the various stages along the cancer continuum. Even prior to diagnosis, some women are turning to CAM to relieve the anxiety and pain that is sometimes experienced during diagnostic procedures, which ultimately may affect timely and accurate treatment. One NCCAM-funded investigation recently reported that self-hypnosis during core needle biopsy performed in the diagnosis of breast cancer produced greater relief of anxiety and pain relative to standard care, but it did not significantly increase the time or cost of the procedure. Even after diagnosis, many cancer patients report using CAM therapies, but concurrent use of CAM and conventional therapies raise questions about interactive effects. Some NCCAM clinical research projects are specifically examining the effects of complementary approaches used in the context of conventional treatment, while others compare alternative therapies with conventional treatments. For example, two studies are looking at the use of ginseng as an adjuvant during standard treatment for breast cancer to understand if it aids or interferes with chemotherapy, hormonal therapy, or radiation 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 is examining the effect of acupuncture treatment on chemotherapy-induced neutropenia in women with ovarian cancer. Another study is looking at the use of ginger to control nausea and emesis in patients receiving Adriamycin or cisplatin.

The NCCAM also funds several projects relevant to women with breast cancer. One study is looking at the effects of soy on breast development and cancer risk, while another 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. A mechanistic study is focused on the mechanism by which soy phytochemicals may prevent breast cancer.

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 side effects of conventional treatments and to maintain immune competency. The NCCAM is supporting an exploratory study to compare the effects of healing touch on immune function in advanced cervical cancer.

Many breast cancer patients experience debilitating fatigue while receiving radiation and/or chemotherapy, and, for approximately one third of breast cancer survivors, that fatigue persists long after the completion of treatment, even in the absence of cancer recurrence. No conventional therapy has been found to effectively treat this fatigue. The NCCAM, with support from the ORWH, is funding several clinical studies to explore whether alternative approaches might be effective in this context. One study is comparing the effects of Swedish massage and polarity therapy, a biofield energy therapy, for fatigue in breast cancer patients receiving radiation treatment. Two other studies are exploring the effects of Qi gong and Iyengar yoga for persistent fatigue in women who have completed conventional cancer treatment (other than hormonal therapy) at least six months earlier and are continuing to experience severe, persistent fatigue.

Cardiovascular Disease

Cardiovascular Disease (CVD) is the leading cause of mortality for both men and women in the U.S. More than 500,000 Americans die of heart attacks each year. Approximately 10 percent of women between the ages of 45 and 64 have heart disease; this figure is double in women aged 65 and older. Common conventional medical treatments for CVD can be invasive and costly; some treatments are more risky and less effective for treating CVD of women than men. As the U.S. population turns more frequently to complementary and alternative medicine for a variety of purposes, it is not surprising that such treatments are being used for the symptoms, prevention, and even treatment of CVD. Because of this substantial public use, the NCCAM supports a diverse portfolio of CAM therapies for CVD, including acupuncture and other components of traditional, indigenous systems of medicine, mind-body interventions, such as meditation and yoga, herbal extract treatments, dietary supplements, and several types of energy healing, such as Reiki and Qi gong.

The NCCAM has supported several centers dedicated to investigating the efficacy of CAM therapies for CVD. The University of Michigan CAM Research Center for Cardiovascular Diseases in Ann Arbor was funded to study 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. This center found that the efficacy of these alternative therapies was inconclusive and more research is needed.

The Center for CAM, Minority Aging, and Cardiovascular Disease in Iowa was funded to study Ayurvedic medicine, a form of traditional Indian medicine that incorporates herbal formulations and meditation, to treat CVD in older African Americans. The work at this center included basic research on the mechanisms of meditation on atherosclerotic CVD, 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 antioxidants versus conventional vitamin supple-

mentation on carotid atherosclerosis and other CVD risk factors. The researchers found that transcendental meditation may be effective in reducing carotid artery intima medial thickness and improving functional capacity among individuals at high risk for CVD and that the program is a cost-effective method for reducing the risk and progression of CVD.

The Oregon State University Center of Excellence for Research on CAM Antioxidant Therapies is currently funded by the NCCAM to conduct studies using cell cultures and animal models to determine the molecular and cellular mechanisms of action and in vivo safety and efficacy of selected antioxidant therapies in CVD. Although research is still ongoing, the center found in its preliminary work that lipoic acid inhibits LPS-induced inflammation and that chelation has no effect on serum cholesterol and triglyceride concentration.

The NCCAM, with funding from the ODS, supports the Center for Botanical Lipids at Wake Forest University Health Sciences. This center conducts studies to examine biological mechanisms and clinical applications of botanical sources of polyunsaturated fatty acids that may have benefit in the prevention and treatment of anti-inflammatory diseases, such as atherosclerosis.

The Botanicals Research Center for Age-related Diseases at Purdue University, co-funded by the NCCAM and the ODS, is a multidisciplinary team of scientists conducting research on botanicals as dietary supplements for age-related diseases, such as heart disease. The focus of the center is on polyphenols, a diverse group of chemical components widely distributed in plants that act as antioxidants but may also have other biological actions.

NCCAM also supports a number of studies looking at the effects of various CAM therapies on those at increased risk for subsequent CVD. For example, the NCCAM supports an investigation of the efficacy of meditation among individuals at risk for the development of essential hypertension. A grant to systematically assess the efficacy of yoga among women at risk for the development of CVD is being carried out with support from the NCCAM and the ORWH. Further work is ongoing regarding the effects of tai chi on functional capacity, neuro-hormonal status, and autonomic tone among heart failure patients, and investigation of the effects of acupuncture on autonomic function, inflammation, and arterial vasomotor activity in cardiac patients. With funding from the ORWH and the ODS, the NCCAM is supporting a randomized, double-blind, placebo-controlled trial of phytoestrogens on the progression of carotid artery intima-media thickness and CHD risk, lipids, and inflammatory markers.

Obesity

Obesity is an epidemic among women, especially among non-white racial and ethnic groups. Obesity and overweight are known risk factors for a number of diseases, and the health benefits of weight loss are well established. National dietary weight loss guidelines have been challenged by proponents of CAM diets, especially low-carbohydrate diets. However, the effects of these diets on short- and long-term weight loss and disease risk are unknown. The NCCAM supports several studies of CAM diets. Results from one of these were recently reported. A 12-month randomized trial was conducted from 2003 to 2005 at Stanford University Medical School among 311 overweight/obese, nondiabetic, premenopausal women. The participants were randomized to the Atkins, Zone, LEARN (based on national guidelines), and Ornish diets. Weight loss was greatest in the Atkins diet group compared with the other diet groups at 12 months, and there was no difference among the other three groups. The adverse metabolic effects of low-carbohydrate diets were not substantiated. The authors concluded the long-term effects and mechanisms remain to be determined. The NCCAM is currently supporting two studies of the long-term (up to 2.5 years) effects of low-carbohydrate diets, as well as a feeding study to assess the impact of low-carbohydrate diets on hormones and other factors that regulate appetite and energy balance.

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 (E. 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, NCCAM sought a contractor to develop standardized cranberry juice cocktail, a necessary antecedent step for a clinical trial. In 2005, the clinical studies began enrolling participants. The last of these four studies will complete followup in 2010. In addition, pharmacokinetics and drug interaction studies, as well as investigations of animal models, are ongoing.

Initiatives

Request for Applications (RFAs)

- **Improving Measurement Tools for Sternal Skin Conductance**
  The NCCAM has several initiatives related to menopause. Vasomotor symptoms, including hot flashes and night sweats, are frequently reported by menopausal women (as well as breast cancer survivors and men undergoing androgen deprivation therapy.) In the wake of the findings from the Women's Health Initiative, many women are turning to non-hormonal means to manage hot flashes and other symptoms of menopause, including complementary and alternative medicine. There is a long history of use of CAM therapies for menopausal symptoms, but the empirical base to assess safety and efficacy is neither extensive nor very strong. 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. The NCCAM supported four studies under this RFA for the development of improved sternal skin conductance monitors for use in ambulatory settings to capture frequency data on hot flashes. This RFA addressed the need for improved tools, which could collect more data and perform better in unsupervised, ambulatory conditions. Such tools are needed for improved efficiency and economy of future clinical trials of CAM therapies to reduce hot flashes. (RFA-AT-05-005)

- **Tools and Technologies to Measure Menopausal Symptomatology**
  Sternal skin conductance monitors are not able to capture all dimensions of hot flashes, such as intensity and interference with daily life, nor are they able to collect data on other symptom domains of menopause, such as affective, somatic, and urogenital symptoms. Various questionnaires and diaries have been used in previous studies of menopause, but many have not been validated in different subpopulations of interest to clinical investigators. Moreover, there are only limited data on automated data collection systems used in clinical studies of menopause, such as computer-assisted self-interviews (CASI). Such systems afford important economies in data collection and analysis, including automated skip patterns, data range checks, and transfer of data to systems for analysis. This RFA was issued to encourage small businesses to develop improved instruments and devices to collect self-reported data on the broader domains of menopausal symptoms. Improved sternal skin conductance monitors should be used to validate self-reported measures of hot flash frequency. Collaboration with clinical investigators who understand the construction of self reported instruments, their validation and testing, is critical. Investigators with improved sternal skin conductance monitors were invited to apply to develop instruments and tools to collect self-reported measures of the range of symptoms associated with menopause and targeted by CAM therapies. Three grants were made. Through these initiatives, we anticipate the availability of new and innovative technology in future clinical studies of CAM treatments for hot flashes. (RFA-AT-06-003)

The NCCAM has enjoyed and benefited from its relationship with the ORWH and looks forward to continued collaborative activities.

Health Disparities among Special Populations of Women

The NCCAM is committed to studies focused on reducing and eliminating health disparities among our most vulnerable populations, particularly racial and ethnic minorities. The NCCAM is focusing on diseases, like asthma and arthritis, which are more prevalent or more severe in minorities, as well as studying why and how ethnic and racial minority populations use CAM. Some examples of such studies are an NCCAM-funded investigation of symptoms and attitudes of menopause among the Q'eqchi Maya of the eastern tropical lowlands of Guatemala, and a study of ethnic variation in the arachidonate 5-lipoxygenase (ALOX5) gene to identify individuals who may derive greater benefit from omega-3 fatty acid supplementation. Because most of our existing knowledge regarding how and when CAM is used is based on investigations of white, non-Hispanic adults, NCCAM is funding an investigation comparing the use of herbal medicine and dietary supplements among white, African American, Hispanic, and Chinese populations. The NCCAM also is funding a study to delineate the use of CAM among Hispanics living in the U.S. and Mexico.

National Center for Research Resources

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the environments and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support enables discoveries that begin at a molecular and cellular level to move to animal-based studies and on to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. The NCRR connects researchers with one another as well as with patients and communities across the nation to harness the power of shared resources and research. The NCRR develops and supports biomedical resources that include sophisticated 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; state-of-the-art equipment available on a shared basis; strong research infrastructure for predominantly minority institutions; infrastructure enhancement and mentorship at institutions in states with little history of NIH funding; and 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 to address emerging clinical and basic research needs. The NCRR is leading a national consortium—funded through Clinical and Translational Science Awards—that will transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients.

The recent accomplishments in women's health research described below exemplify the breadth of science and technology supported by the NCRR to promote understanding of normal and abnormal physiology in women. In addition, the NCRR supports research on the prevention and treatment of diseases, disorders, or conditions that are unique to women or have a significant impact on women. Accomplishments highlighted in the following 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

Research and Center Activities in Women's Health

The NCRR provides high quality, disease-free animal models and biological material resources for biomedical investigators. This is accomplished by supporting centers that breed

and make such models available to researchers interested in women's health issues, among other research topics. Specifically, non-human primate models and genetically engineered mice allow for research on women's diseases and related conditions. Such research has been supported for conditions affecting female reproductive organs, menopause, contraception, questions related to reproductive endocrinology, and osteoporosis. Furthermore, breeding facilities provide opportunities for research on reproductive physiology and pathology. Finally, the NCRR supports women scientists through its veterinary training programs enabling women to advance their professional careers in the veterinary sciences.

Supported by the Institutional Development Award (IDeA) as part of its Centers of Biomedical Research Excellence (COBRE) program, a Center of Biomedical Research Excellence for Perinatal Biology at the Women and Infants' Hospital of Rhode Island contains research core activities in tissue imaging, laser capture micro-dissection, and real-time PCR for quantification of gene expression, at the level of cellular resolution. It also is engaged in 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 development 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. Development of a tractable animal model 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.

Women's health research is also supported by the COBRE at the University of Kentucky. The present award represents a competitive renewal of the COBRE in Women's Health that was initially funded from 2000 to 2005. The two primary goals of the COBRE in Women's Health are to: (1) further our understanding of the unique role of gender and female reproductive hormones in the manifestation of health and disease, and (2) use this focus as a platform to develop promising junior investigators and enhance their success in competing for NIH grant support. A unique strength of the COBRE in Women's Health research is the multidisciplinary approach to investigate the impact of hormones and gender on five specific areas: heart disease, brain function, HIV, reproductive tract physiology, and behavior. Each of these five areas will be explored by a team of investigators. These teams bring together 21 faculty members with diverse interests and research backgrounds from the Colleges of Medicine and Allied Health, highlighting the true multidisciplinary approach of the COBRE program to further our understanding of the role of hormones and gender in key areas of women's health.

The NCRR made a grant award to renovate 9,696 square feet of space in the old Hubbard Hospital of Meharry Medical College to establish a Center for Women's Health Research (CWHR). This renovated space will house a laboratory equipped for human cell biology studies; core facilities for endocrine assays, monitored exercise, radiological studies and behavioral studies, and one examination room. These renovations will consolidate research on health issues that disproportionately affect women of color conducted by investigators in the departments of obstetrics and gynecology and psychiatry. The two foci of these studies are sexual and reproductive health and socio-behavioral dimensions of HIV/AIDS. Over the next three to five years, the CWHR will strengthen these foci and enrich them by recruiting investigators in three other research areas represented at the college: breast cancer, health care access and quality, and social and environmental factors in women's health. In addition to housing facilities for experimentation in the two focus areas, the renovated areas of the center will provide a locus for scientific exchange among investigators in women's health by means of seminars and colloquia and will provide a research-training center for students, residents, and faculty in women's health. The renovation project is in the construction phase and will be completed in FY 2009.

NCRR Career Development Activities and Programs

In FY 2005 and 2006, the NCRR sponsored two symposia highlighting scientific endeavors of prominent women scientists. The 10th Annual Maria Goeppert-Mayer Symposium was held on March 5, 2005, and the 11th Annual Maria Goeppert-Mayer Symposium was held on April 7-8, 2006 at the University of California, San Diego (UCSD). Partial funding for the symposia was provided through the National Biomedical Computational Resource at UCSD, which is an NCRR-funded resource. A primary goal of this activity is to promote academic and industrial career development for women in science.

The K99/R00 Pathway to Independence Award allows promising postdoctoral scientists the opportunity to receive both mentored (K) and independent research support (R) from the same award. The K01 Special Emphasis Research Career Award (SERCA) in Pathology and Comparative Medicine, a Mentored Research Scientist Development Award, assists graduate veterinarians to become independent investigators in research related to comparative medicine. The K26 Mid-career Investigator Award in mouse pathobiology research provides support for established mid-career mouse pathobiologists, affording them protected time to devote to research involving mice and to act as mentors for beginning investigators. The T32 and T35 Training Grants also provide opportunities for career development, providing long- and short-term support for training highly qualified veterinarians and veterinary students for research careers in biomedical areas related to comparative medicine, comparative pathology, or research related to applications that improve and extend healthy lives and prevent illness. Women are well represented in all programs both as mentors and trainees. One hundred percent of the current K99/R00 awards have female PIs. In the K01 program, 48 percent of the Division of Comparative Medicine (DCM) awards are made to women. Many of the top veterinary colleges have female PIs leading the T32 and T35 mentoring/ training programs. Women represent approximately 85 percent of the trainees in these programs.

The Division of Research Infrastructure administers the Clinical Research Education and Career Development (CRECD) awards to develop and implement curriculum-dependent programs in minority institutions to train selected doctoral and postdoctoral candidates in clinical research. The programs lead to a master of science degree in clinical research or a masters of public health degree in a clinically relevant area. The goal of the program is to promote the development of well-trained and independent clinical researchers who can lead clinical research studies addressing health disparities among the American people. The CRECD program provides multidisciplinary, didactic training for clinical research as well as mentored clinical research training to enhance clinical research skills. The CRECD program is a trans-NIH program co-funded by the NCRR, the NCMHD, the NEI, the NHLBI, the NIA, the NIAMS, the NIDA, and the NIDDK. In the CRECD Program, approximately 70 percent of the trainees are minority women.

The NCRR supports a Roadmap K12 Multidisciplinary Clinical Research Career Development Programs (MCRCP) at the University of Wisconsin, Madison that has initiated the Training and Education to Advance Multidisciplinary (TEAM) and Clinical Research Program. The TEAM Program clinical research scholars conduct translational research in disciplines ranging from nursing to bioengineering. The program has also been successful in increasing the participation and advancement of women and underrepresented minority researchers in clinical research.

The Mayo Clinic College of Medicine in Rochester instituted a multidisciplinary General Clinical Research Center (GCRC) 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.

Research Accomplishments: Highlights

- **Slowing the Spread of HIV/AIDS—Microbicides**

  The development of effective microbicides has been one approach to finding a method to prevent sexual transmission of HIV and other pathogens. Testing of broad spectrum microbicides has had disappointing results, suggesting that more targeted approaches may be necessary. NCRR-funded scientists at the Tulane National Primate Research Center have tested a novel type of microbicide in rhesus monkeys using the SIV model. This microbicide, termed a "fusion inhibitor," prevents the virus from binding to a specific receptor on vaginal cells, thus potentially inhibiting entry of the virus into the body. These microbicides are made up of several peptides and small molecules that inhibit attachment and entry by blocking receptors on both the virus and host cell. Results have shown protection even when applied six hours prior to challenge with the virus. One of these small molecules was also tested by oral administration prior to exposure to the virus. A high percentage of these animals were protected from infection. Animal subjects that were infected had significantly reduced plasma viral levels relative to experimental controls.

  Researchers at the NCRR-supported Comprehensive Center for HIV/AIDS Disparities at Meharry Medical College are conducting preclinical studies of an effective yet inexpensive topical microbicide, beta cytodextrin. Beta cyclodextrins are simple polymer sugars widely used in a variety of products, including mouthwashes, topical creams, food flavorings, and intravenous medications. Researchers at Meharry Medical College have demonstrated that beta cyclodextrins deplete cholesterol from both HIV and host cell members, thereby preventing cell-to-cell transfer of HIV in mouse models. Plans are underway to advance this microbicide candidate to clinical trials at Meharry's Clinical Research Center, supported by an NCRR grant from the Research Centers in Minority Institutions (RCMI) Program.

  Researchers at the NCRR-supported GCRC at the Mount Sinai School of Medicine in New York recently showed that the environment of the human vagina does not lessen the potency of PRO 2000/5, a sulfated polyanion vaginal microbicide designed to inhibit viral entry of HIV into susceptible cells. Moreover, when human cells were inoculated with the cervicovaginal samples, the PRO 2000/5 inhibited both HIV and herpes simplex virus (HSV) infection by at least 1,000-fold. In a followup study involving 24 healthy women, daily applications of PRO 2000/5 did not trigger an inflammatory response in cervicovaginal secretions, suggesting that repeated use of this microbicide is safe. Investigators in the GCRC at Mt. Sinai are currently conducting clinical trials to evaluate the safety and ability of PRO 2000/5 to prevent HIV infection in at risk women.

- **Polycystic Ovary Syndrome (PCOS)**

  PCOS is a health problem that can affect a woman's menstrual cycle, fertility, hormones, insulin production, heart, blood vessels, and appearance. Women with PCOS have the following characteristics: high levels of male hormones called androgens, irregular or no menstrual cycles, and possible formation of large numbers of small cysts in their ovaries. PCOS is the most common hormonal reproductive problem in women of childbearing age. NCRR-funded researchers at the California and Wisconsin National Primate Research Centers, as part of the Northwestern University Specialized Center of Research on Sex and Gender Factors Affecting Women's Health, are conducting studies on the etiology of PCOS, including determining the gene region associated with this syndrome and the role that prenatal androgen excess plays in its development. These studies are conducted using the rhesus monkey model. Results indicate that early gestation androgen excess induces luteinizing hormone (LH) hyper-secretion, which later induces one component of the reproductive abnormalities found in PCOS women. These studies aim to identify fetal and neonatal markers for PCOS to gain a better understanding of the mechanisms of this condition.

- **RU486 to Treat Ovarian Cancer**
  Ovarian cancer (OCa) is the leading cause of death in women from gynecologic diseases, in part because of the difficulty in performing early diagnosis. However, mortality is also due to the lack of successful treatment strategies. Investigators at the NCRR-funded Biomedical Research Infrastructure Network at the University of South Dakota, Vermilion are investigating the feasibility of using the progesterone receptor modulator mifepristone (MF), which is popularly known as RU486, as a therapeutic tool for OCa. The general hypothesis of this research is that MF can function as a broad therapeutic agent for OCa, targeting three different facets of the disease. The researchers have demonstrated that MF is a potent cytostatic agent for OCa cells. They have demonstrated that MF accelerates the activation of a cell death mediator when induced by the platinum compound cisplatin, suggesting that MF sensitizes OCa cells to the cytotoxic effect of cisplatin. They have also generated data demonstrating that treatment with MF substantially alters the morphology of OCa cells and impairs their capacity to adhere to tissue outside the cell, highlighting the potential for using MF as an anti-metastatic agent in OCa.
- **Identification of Cellular Markers of Cervical Neoplasia Using Parallel Genomics and Proteomics Approaches**
  Investigators at the RCMI Clinical Research Center at Meharry Medical College are researching two complementary but independent approaches to identify more rapidly potential cellular markers of cervical neoplasia. First, a molecular genomic approach that utilizes serial analysis of gene expression (SAGE) methodology is used to quantify mRNA transcript levels and compare transcript abundance between normal cervical tissue and squamous cell carcinoma. SAGE is a powerful approach that permits the identification of every expressed gene, including novel genes within the human genome that may not be included on standard microarrays. Second, a proteomics-based approach, which utilizes mass spectroscopy, is pursued in parallel, providing a unique comparison when the resulting data are analyzed. The technical feasibility of both molecular and proteomic approaches has already been established within the investigator's laboratories. This approach will allow for rapid identification of promising biomarkers and validation of markers used in diagnostic screening applications.
- **Hormonal Characteristics of the Perimenopausal Transition**
  This NCRR funded study uses cynomologous monkeys (Macaca fascicularis) exposed to 4-vinylcyclohexene diepoxide, which selectively destroys ovarian primordial and primary follicles, to establish a model for menopause. Emerging evidence suggests that menopausal conditions, such as CVD, osteoporosis, and cognitive decline, originate in the premenopause period, especially during the several years that precede menopausal transition, which are characterized by fluctuating and declining ovarian hormone production. This research aims to define the hormone characteristics of the perimenopausal transition, subsequent menopause, and the resulting changes in risk markers for chronic diseases, such as atherosclerosis and osteoporosis. Not only does this research provide insight into the changes associated with menopause, but it also provides the research community with an animal model to study this transition.

Initiatives

The NCRR did not issue any specific Requests for Applications, Requests for Proposals, Program Announcements, or workshops in the area of women's health in FY 2005 or 2006. However, through its support of unique resources, 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 priorities. Therefore, future increases in women's health and behavior research supported by other components of NIH will result in corresponding NCRR increases.

Health Disparities among Special Populations of Women

Parameters of the Menopausal Transition in Hispanic Women in Puerto RicoParameters of the Menopausal Transition in Hispanic Women in Puerto Rico

The University of Puerto Rico Medical Science Campus, with the support from NCRR's Research Centers in Minority Institutions (RCMI) 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 include 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, CVD, and osteoporosis are assessed by a self-reported questionnaire. Associated factors considered in this research include obesity, smoking, exercise patterns, calcium intake, alcohol intake, and medication use. The study has a particular focus on the influence of lifestyle patterns and stage of menopause on the annual rate of change in bone density. Bone ultrasound of the calcaneous and DEXA of the hip and spine are performed to assess the prevalence and severity of osteopenia and osteoporosis. Bioelectrical impedance is utilized to assess body composition and its association with both the experience of menopausal symptoms and osteoporosis. The study also addresses compliance to recommendations given to participants about osteopenia and osteoporosis.

Research on Sex Steroids, Leiomyomas, and Cervical Cancer in African American Women

The RCMI Program supports a number of studies at Meharry Medical College's Center for Women's Health Research. The program provides infrastructure and direct support for the following research projects: studies to determine if elevated sex steroid levels may account for some of the hormone-related conditions that follow throughout life in African American females, including leiomyomas, endocrine related cancers, and protection from osteoporosis; case-control observational studies that directly monitor the growth of uterine leiomyomas in women taking oral contraceptives using serial ultrasound evaluations; and studies to identify cellular markers of cervical neoplasia using molecular genomic and proteomics-based approaches.

The Role of Leptin in Infertility

The relationship between metabolism and reproduction remains a central question in female endocrinology. Leptin, a protein hormone decoded from the obesity (ob) gene, is secreted from adipose tissue and acts on the central nervous system to result in the suppression of food intake and increase energy consumption. It is also known to play an important role in pubertal development and reproductive capacity, and it has been shown to be present at reduced levels in anorectic women. Investigators at the RCMI program 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.

Comprehensive Centers on Health Disparities (CCHDs) in HIV/AIDS

The primary goals of the NCRR-funded CCHDs are to: (1) develop sustainable, replicable, and culturally appropriate prevention and/or intervention research programs to decrease the incidence and prevalence of disease; (2) strengthen clinical and translational research capacity at minority medical schools committed to addressing health disparities; and (3) enhance opportunities for multidisciplinary research collaborations on health disparities. Comprehensive Centers on HIV/AIDS Disparities in women are funded at Meharry Medical College and in Puerto Rico. African American women account for more than 60 percent of female HIV infections. Therefore, researchers in the Meharry Center aim to pursue avenues to address this

problem by engaging the community in both research and education. The Comprehensive Center for the Study of HIV/AIDS in Puerto Rico is unique and important because, for the first time, the three accredited medical schools (the University of Puerto Rico School of Medicine, Universidad Central del Caribe School of Medicine, and Ponce School of Medicine) collaborate as partners to study topics, such as HIV risk behaviors, stigma, and the impact of violence and abuse in HIV/AIDS prevalence in the Puerto Rican population.

Periodontal Disease, Diabetes, and Preterm Delivery

Preterm delivery is a major health care problem affecting one in 10 births, and it is the leading cause of neonatal death and long-term disability in the U.S. 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. Ethnicity clearly plays a role in both the rate of prematurity and the prevalence of diabetes. In Hawaii, diabetes is particularly prevalent and a major health problem for Pacific Islanders. 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. These studies are continuing to determine which organisms are involved in periodontal disease in pregnant diabetic and non-diabetic Asian and Pacific Islander women and if acute infections involving the genitourinary tract or distant organs are implicated in preterm birth. Thus, 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.

Genetic Polymorphisms and Preeclampsia

The University of North Dakota School of Medicine and Health Sciences, with the support from NCRR's IDeA Networks of Biomedical Research Excellence (INBRE) Program, conducts genetic research focused on health problems of special interest for the Turtle Mountain American Indian community. One study focuses on pregnancies that are complicated by high blood pressure, abnormal protein in the urine, and other signs, which together are called preeclampsia. In this study, risk factors and specific genetic polymorphisms associated with preeclampsia in the Turtle Mountain community will be identified. This research will be conducted in collaboration with the tribal government, the Indian Health Service, and community members.

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 survey instruments useful in generating data to address disparities in health for African Americans and Hispanics in the areas of diabetes, chronic kidney disease, menopause, and hormone therapy among African American and Hispanic women. This core also supports research focusing on stress reduction and atherosclerotic CVD morbidity and mortality in African American women.

Gender Analysis

Through its unique role in providing technologies, equipment, building renovations, training opportunities, and infrastructure 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 are described above.

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 multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information, promote research infrastructure and training; foster emerging programs; and extend its reach to minority and other health disparity communities. 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 supports the Research Infrastructure in Minority Institutions Program (RIMI) and the Minority Health and Health Disparities International Research Training Program (MHIRT). These combined efforts position the NCMHD to lead and coordinate the NIH health disparities activities for the benefit all affected populations, including women of diverse populations.

- **The NCMHD Loan Repayment Program**
  The NCMHD has two distinct loan repayment programs: 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 the Extramural Clinical Research Program, which supports the recruitment and retention of health professionals from disadvantaged backgrounds to conduct clinical research.
- **The NCMHD Centers of Excellence Program**
  This program funds Centers of Excellence that conduct research, research training, and community outreach activities relevant to health disparities. These centers advance the science related to health disparities; create, develop and evaluate new interventions for preventing, reducing, and eliminating health disparities; and disseminate to health disparity communities information useful for improving health.
- **The NCMHD Research Endowment Program**
  This program builds research and training capacity in institutions that significantly invest 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.
- **The NCMHD Research Infrastructure in Minority Institutions Program (RIMI)**
  This program helps institutions that enroll a significant number of students from minority health disparity populations develop and enhance their capacity and their competitiveness to conduct biomedical research. The RIMI program also assists non-doctoral degree institutions in developing their research infrastructure, primarily through collaborations with research-intensive universities.
- **The NCMHD Minority Health and Health Disparities International Research Training (MHIRT) Program**
  This program enables U.S. institutions to offer qualified eligible students in basic, biomedical, clinical or behavioral science short-term international research training opportunities that 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, a five-year strategy and accompanying budget that guides the NIH research agenda for combating health disparities. In fiscal year 2004, the NIH Committee on Minority Health and Health Disparities Research Definitions and Application Methodology developed a new definition for minority health and health disparities and consistent guidelines. The NIH

Institutes and Centers (ICs) will use this guidance, which now includes low socioeconomic status and rural populations when reporting on minority health and health disparities activities.

Accomplishments

This report highlights examples of women's health projects supported by the NCMHD in FY 2005 and 2006 through its Centers of Excellence Program, Loan Repayment Program, Minority Health and Health Disparities International Research Training Program, and partnerships with the other NIH Institutes and Centers (ICs).

NCMHD Centers of Excellence Program

In 2005, the NCMHD entered its fourth year of funding under this program. Examples of women's health research and programs include the following:

- **Reducing Underuse of Early-stage Breast Cancer Treatment in Minority Communities**
  This project is assessing the extent of underuse 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 the underuse 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 and patient and physician reasons for underuse 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 more than 1,000 identified breast cancer cases from six different hospitals. In a cross-sectional study of the medical records of nearly 677 women, 145 (21 percent) experienced underuse of appropriate adjuvant therapy: 16 percent in whites, 34 percent in blacks, and 23 percent in Hispanics. Women referred to medical oncologists were less likely to experience underuse of necessary adjuvant treatments. Women who were minorities had higher levels of co-morbidity and lacked insurance were at greater risk for underuse. Researchers concluded that minority women with early-stage breast cancer have double the risk of white women for failing to receive necessary adjuvant treatments despite rates of oncologic consultation similar to those for white women. Oncology referrals are necessary to reduce treatment disparities but are not sufficient to ensure patients' receipt of efficacious adjuvant treatment. (Bickell, N.A., et al. *Journal of Clinical Oncology* 24:1359-1362, 2006)

- **African American Child-Women: Nutrition Theory Revisited**
  Past research indicates a significantly higher prevalence of early sexual maturation in African American girls, which is associated with a number of psychological and behavioral problems, as well as with health problems, such as childhood obesity and diabetes. Both nutrition and body image perceptions have never before been empirically investigated in the context of early puberty. The present study analyzed nutritional differences among African American girls who experience early sexual maturation and those who do not, as well as the dynamics of early sexual maturation, food consumption, and body image perceptions of African American girls. Participants were 45 African American girls, ages seven to 10 years, and guardians who were recruited from Boys and Girls Clubs in the southeastern part of the U.S. The Continuing Survey of Food Intakes by Individuals and Fallon and Rozin's (1985) Body Image Checklist were used to assess the food intake and body image perceptions of the young girls. Evidence of early sexual maturation was operationalized as the parental report of development of any secondary sexual characteristics (breasts, hips, pubic hair) in the young girl. A two-day food intake recall was conducted over a representative weekday period. Results revealed a significant difference between the calcium and fiber consumption of the African American girls who experienced early sexual maturation versus those who did not. Also results indicated a relationship between parental characteristics, household shopping practices, and food consumption of the young

girls. These findings are important and can be used to predict, prepare, and educate the African American population as well as establish appropriate support systems for these child-women. (Talpade, M. *Adolescence* 41:91-102, 2006)

- **African Americans and Participation in Clinical Trials: Differences in Beliefs and Attitudes by Gender**
  The purpose of this study is to explore gender differences in perceptions of: (1) barriers and motivators to participation in clinical trials and perceived need of clinical trials; and (2) perceptions of risks and benefits of participation in clinical trials in African American men and women. Focus groups were conducted among African American participants by gender. A total of 67 African Americans participated in the focus groups. All focus groups were audiotaped and transcribed verbatim. Different themes emerged for men versus women. The business and economic of research were important to male participants. The researcher-participant relationship emerged as one of the strongest themes related to potential female participation in research. Focus group results indicate that African American men and women present different preferences, beliefs, and barriers to participation. Men expressed the desire to know information about funding issues, financial benefits, and impact of the research. Women expressed the desire to be treated respectfully and as an individual as opposed to just as a study subject. Integrating gender preferences into researcher-participant interactions, advertisement, informed consent delivery, and advertisement of research studies may lead to increased participation rates. Discussing and presenting relevant information on clinical research funding mechanisms, and the business of clinical research with potential participants may be helpful in building trust with the researcher and the research team. Creating a process for information exchange and methods to minimize the power imbalance between the researcher and participant may also build trust and help participants feel more comfortable to participate in research. (BeLue, R., et al. *Contemporary Clinical Trials* 27: 498-505, 2006)

The NCMHD Loan Repayment Program

Since FY 2005 and 2006, the loan repayment program has funded more than 50 researchers conducting research related to women's health, including the following examples:

- **Gender-based Differences in Fertility Beliefs and Knowledge among Adolescents from High Sexually Transmitted Disease-Prevalence Communities**
  Limited information is available about adolescents' beliefs about fertility in women and its link to sexually transmitted disease (STD) and whether men and women differ in their beliefs. This information may be useful for developing messages intended to motivate youth to seek STD screening while they are asymptomatic. This study examined gender-based differences in fertility beliefs and knowledge. Data were derived from the Adolescent Health Study, a population-based telephone survey study in which urban household adolescents from a high STD-prevalence community were queried about their sexual experience, fertility-related knowledge, beliefs related to timing of childbearing, and risk assessment of future fertility problems. Chi square and regression analyses were used to evaluate group differences. The majority of adolescents reported that having children was somewhat or very important, but that the 15- to 19-year-old age group was not the optimal time for a woman to have a child. Regression analyses indicated that female adolescents were more likely than male adolescents to identify chlamydia and pelvic inflammatory disease as causes of fertility problems. Seventy-two percent of adolescent girls thought there was some chance they would have future fertility problems and 59 percent thought they had little or no control over developing fertility problems in the future. Additional health education is needed if we are to motivate adolescents to participate in asymptomatic STD screening programs. Involving male adolescents may be a more significant challenge given that fewer male adolescents understand the link between female fertility and common STD-related conditions.

Given our findings, fertility preservation may be a valuable teaching tool and social marketing agent for STD prevention in adolescents.

- **The Relationship between BMI and LPS-stimulated TNF-a and IL-6 Production in African American Women**
  Obesity is associated with an increase in chronic, low-grade inflammation. Chronic inflammation has been implicated in the development of type 2 diabetes mellitus and cardiovascular disease. The primary purpose of this study was to determine whether obesity status differentially altered whole blood LPS-stimulated IL-6 and TNF-α production *in vitro*. Twenty-four African American women were recruited for the present investigation from a larger study and distributed to one of five groups based on BMI: normal weight (NW; BMI 20-25), overweight (OV; BMI 25-30), class one obese (1OB; BMI 30-35), class two obese (2OB; BMI 35-40), or class three obese (3OB; BMI >40). Body composition was determined via a whole body DXA scan. Venous blood samples were collected following an overnight fast (more than eight hours), diluted (1:20 in RPMI 1640), and stimulated with five doses of lipopolysaccharide (LPS, from Salmonella enteritidis): 80, 40, 20, 10, and 5 μg/m L-1 for 24 hours in a 37°C, 5 percent carbon dioxide incubator. Following stimulation, cell-free supernatants were analyzed in duplicate for IL-6 and TNF-α using separate enzyme linked immunosorbent assays (ELISAs). Data were analyzed for significance using a one factor analysis of variance. No significant group differences were found for LPS dose with either TNF-α or IL-6 production. Due to lack of significant LPS dose effects, maximal TNF-α and IL-6 production was compared among groups. The 3OB group had significantly greater maximal TNF-α production than other groups (P=0.012). No significant group effects were found for maximal IL-6 production. Body weight and BMI were significantly correlated with maximal TNF-α (rs=0.55, 0.53) and IL-6 (is=0.51, 0.51) production. These findings are consistent with previous reports suggesting a relationship between increased obesity and monocyte inflammatory capacity. This is one of the first studies to test this relationship in African American women, who have higher rates of obesity. This study did not find different LPS dose effects in individuals of differing BMI, which was contrary to the research hypothesis. More research is needed to evaluate mechanisms responsible for an obesity induced increase in monocyte inflammatory capacity.

- **A Rural and Urban Women Multiple Prospective Study of Protective Order Violation Consequences, Responses, and Costs**
  Intimate partner violence affects thousands of women each year and results in substantial personal and societal costs. In response to the need to protect victims, states have established protective orders. However, the actual effectiveness of civil protective order remains largely unexamined. For these justice system policies to be widely endorsed and assertively enforced, there needs to be evidence that the policy is both effective and cost efficient. This study addresses these two critical gaps in the research literature on civil protective orders by identifying the factors associated with effectiveness of protective order enforcement, and by assessing justice system costs associated with partner violence, protective orders, and differential responses to protective order violations. This study will triangulate the sources of information (using victim self-reports, key informant interviews, and court data on offenders) to address the major questions for this study. Specifically, the aims of this study are to: (1) follow 105 rural and 105 urban women at baseline, three months and six months after receiving a protective order to examine partner violence six months before obtaining a protective order, as well as violations, consequences of violations, justice system responses, and outcomes of justice system responses six months after obtaining a protective order; (2) describe the civil and criminal system histories and responses to protective order violations using official records on protective order respondents in the cases corresponding to the rural (n=105) and urban (n=105) women who participate in the study; (3) examine key informant (n=140) perceptions of deci-

sion factors associated with responses to protective order violations from four main perspectives: individual victim, police, prosecution, and judges, using bounded rational theory to guide interviews; (4) identify the primary case, incident, and community characteristics influencing civil and criminal justice system responses to protective order violations in two rural and one urban jurisdiction; and (5) examine personal and social costs of ongoing partner violence, including justice system costs, six months before and six months after a protective order is obtained for 210 rural and urban women to better understand the full spectrum of costs associated with partner violence, as well as costs associated with differential justice system responses to protective order violations. This study will advance knowledge about protective order enforcement and costs, and will inform policies and practice to increase the effectiveness of protective orders and ultimately the safety of women threatened by partner violence in rural and urban jurisdictions. This project is currently in the data collection phase.

- **Alcohol, Violence, and Health Services among Rural Women**

  Alcohol use and intimate violence are significant public health problems for women that contribute to injury, poor health, mental illness, and disability. This project seeks to understand the role alcohol use may play in both health service utilization and victimization experiences by using baseline and followup interviews as well as event history data collection and analysis with intimate violence victims. Further, limited research indicates that the incidence of intimate violence across geographic areas may be similar. However, the qualitative experiences of intimate violence victims may differ across geographic areas. Within this context, the overall aim of this study is to examine the effect of alcohol on the nature, extent, and co-occurrence of health-service utilization over time among rural and urban women who have a protective order for intimate violence. This proposal is consistent with, and specifically addresses several research objectives in the NIAAA Health Services Research on Alcohol-Related Problems PA# PAS-98-037, including identifying the factors that impede or facilitate the receipt of care by different client populations; defining the characteristics of the treatment services received by those client populations; examining factors and interactions of factors that affect access to and utilization of alcohol treatment; and examining health service utilization patterns and factors that may affect health service utilization. The specific aims for this project are to: (1) 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) 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) 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) examine changes in alcohol use, intimate violence victimization, and health service utilization over a one-year period from baseline to followup among rural and urban women who have a protective orders. This project is currently in the data analysis phase.

- **Improvement of Mammography Referral Implementation among African American Women**

  It is known that low-income women suffer disproportionate breast cancer morbidity and mortality. With support from the Susan G. Komen Breast Cancer Foundation, this study will identify factors related to successful completion and followup of mammography for indigent African American women. This is a longitudinal, descriptive, exploratory pilot study of all women who are 40 years of age or older who had no documented mammogram within the last year at two East Side SUNYAB Department of Family Medicine clinics. A progressive intervention will be

used including a baseline questionnaire, mammography referral flags on patient charts, and a telephone interview three months after mammography referral to ascertain mammogram status and barriers to completion. The main outcome is the rate of mammogram completion and barriers to completion. Of 304 eligible women, 177 consented to participate. The majority reported a total household income of less than $20,000, 89 percent self-identified as African American. Approximately 20 percent reported a previous bad experience with mammography (mostly pain), with nearly one-quarter of these women never receiving another mammogram. Despite physician reminders, only 46 percent of participants received a mammography referral. Physicians cited the non-preventive nature of the visit as their primary reason for non-referral. Of the referred women who were reached for three-month followup, 56 percent had not completed their mammogram. These women cited lack of time as their primary barrier. Fewer than 10 percent cited transportation or cost as barriers. This study supports both provider- and patient-focused interventions to assure mammography completion among low-income African American women.

NCMHD MHIRT Projects

Several MHIRT programs are focused on women's health and on promoting maternal/child health. These studies are being conducted at several research institutions, including the University of Washington, Tulane University, and the University of Alabama at Birmingham. These studies are investigating factors that are associated with the development of cervical cancer and are identifying risk factors for infant mortality and the socioeconomic correlates of birth weight. Regarding cervical cancer research, MHIRT trainees have investigated the role of HPV in the development of cervical cancer and assessed the effectiveness of cervical screening programs in various international settings.

NCMHD Collaborations

The NCMHD works with the other NIH institutes and centers to leverage its resources for addressing health disparities in a broad spectrum of disciplines. Some women's health projects include the following:

The Sister Study

The Sister Study is a project co-funded by the NIEHS and the NCMHD. It 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 three years, 50,000 women who live in the U.S. 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. Over the past two years, most of the recruitment resources and efforts have gone toward recruiting women from diverse groups, but the cohort is still 90 percent white. Although researchers have doubled the proportion of women enrolling each month from diverse groups, the number is still not as high as they would like. The Sister Study has collected 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 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 are weighed and measured and fill out several questionnaires. Researchers 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.

Trichomonas Vaginalis Genetic Analysis of Cell Adherence

The NCMHD co-funds this research study in conjunction with the NIAID. Trichomonas vaginalis is responsible for serious health consequences for women. Significantly, the infection by this parasite is a cofactor 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 that: (1) iron regulates gene expression, compartmentalization and surface placement of all members of the ap65 gene family; (2) there is cross signaling by phosphorylation of trichomonads and AP65 following adherence; and (3) there is a quantitative relationship between host epithelial cell receptors for AP65 and levels of cytoadherence.

A Novel HOX Gene Target in Breast Cancer

The NCMHD and the NCI co-fund this 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 study, 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.

Osteoarthritis Initiative

The Osteoarthritis Initiative (OAI), a public-private partnership among the NIH; other NIH partners, including NCMHD; and private industry that seeks to improve the diagnosis and monitoring of OA and foster development of new treatments has released its first set of data. Making this information available to researchers worldwide will expedite the pace of scientific studies and identification of biological and structural markers (biomarkers) for OA. Researchers can analyze the data to form new hypotheses for further study of OA, which is the major cause of activity limitation and disability in older people. Images, including x-rays and magnetic resonance imaging scans, will also be available to researchers upon request. All data are stored with an anonymous identification number to protect the confidentiality of the participants' information. Over the next five years, the OAI will provide an unparalleled, state-of-the-art longitudinal database of images and clinical outcome information to facilitate the discovery of biomarkers for development and progression of OA. In this study, a biomarker would be a physical sign or biological substance that indicates changes in bone or cartilage. Data gathered from participants are available to researchers at http://www.oai.ucsf.edu. The data include symptoms; pain severity; a measure of pain, stiffness, and function known as the WOMAC OA index; walking ability; endurance; balance and strength; nutrition; and prescription medicines and alternative therapies used by the participants. More data will be released early in 2007. Subsequent data will be released at approximately six-month intervals. When complete, the OAI should provide an unparalleled state-of-the-art database showing both the natural progression of the disease and information on imaging and biochemical biomarkers and outcome measures. The four centers taking part in the study and their principal investigators include: (1) The University of Maryland School of Medicine, Baltimore; Marc Hochberg, M.D., M.P.H., in conjunction with Johns Hopkins Bayview Medical Center; Joan Bathon, M.D.; (2) The Ohio State University, Columbus; Rebecca Jackson, M.D.; (3) The University of Pittsburgh; C. Kent Kwoh, M.D.; and (4) Memorial Hospital of Rhode Island, Pawtucket; Charles Eaton, M.D.

Breast Cancer Prognostic Factors/Pathology Study

This population-based molecular-epidemiologic cohort study of factors that predict mortality in women diagnosed with invasive

breast cancer at ages 45 through 79 is co-sponsored by the NCI and the NCMHD. The overall goal of the study is to evaluate patient and tumor characteristics for their relationship with the risk of breast cancer mortality. The proposed cohort consists of 2,337 women diagnosed with a first invasive breast cancer at 45 to 79 years of age during the period 1993-1999, all of whom previously completed an extensive interview regarding exposures before diagnosis and will now be followed for mortality. Telephone interviews and medical record reviews will be used to collect information on exposures after diagnosis, disease recurrences, and treatment details. Tumor characteristics and markers will be assessed in relation to both mortality and patient factors as a basis for understanding determinants of prognosis. The aims of this study are to: (1) determine if patient characteristics and exposures (before and after diagnosis), including some which are potentially modifiable, are related to the risk of dying from breast cancer; (2) determine if patient characteristics and exposures before diagnosis are associated with histopathologic features and tumor markers; (3) assess the relationship of histopathologic factors and tumor markers, including both well characterized prognostic markers and less well-characterized cell cycle proteins, with the risk of dying from breast cancer; (4) build tissue microarrays that will allow rapid assessment of future markers as they are identified; (5) build a comprehensive resource for future ancillary studies. The investigation of tumor and patient characteristics in relation to mortality could provide etiologic and clinical insights regarding determinants of prognosis and help to generate clues regarding the biology of breast cancer progression.

A Training Program in International Women's Health

This study addresses a pressing issue in prevention of mother-to-child transmission (MTCT) of HIV within sub-Saharan Africa. Since the demonstration of intrapartum nevirapine (NVP) as a cheap, simple, and effective means of reducing MTCT, many national programs have incorporated the drug into their standard care. Although the public health benefits cannot be understated, widespread use of NVP in this fashion may come at a cost. Recent work shows NVP resistance may peak at two weeks postingestion, at a frequency as high as 75 percent. Although mutations generally fade to undetectable levels by 12 months using standard assays, there is growing concern that their one-time presence may predict reduced efficacy of NVP, or other non-nucleoside reverse transcriptase inhibitors (NNRTIs), in long-term HAART. It is clear that innovative approaches are needed to address this issue. This randomized trial will investigate what impact the addition of two drugs, zidovudine (ZDV) and lamivudine (3TC), to the standard maternal NVP regimen may have on NNRTI resistance postdelivery. Two NVP-containing regimens will be tested. The first will consist of a single-dose, three-drug combination tablets to be taken at the onset of labor. The second regimen will incorporate the same three-drug combination during labor, along with a 10-day, postpartum course of ZDV/3TC. The third group will utilize the standard NVP regimen as described by HIVNET-012 and serve as a control arm. All infants will receive two mg/kg of NVP syrup. The primary outcome will be the prevalence of HIV resistance mutations at two weeks postpartum. To detect a reduction from 75 percent to 45 percent, 70 participants will be recruited into each arm for a total of 210. Second outcomes include feasibility, frequency of 3TC resistance mutations, and infant HIV transmission at six weeks postpartum. Follow-up will continue to one-year postdelivery.

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 (i.e., glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer on average than men, more women than men are affected by age-related eye diseases in the U.S.

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 and in most cases 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 from age or trauma; 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 than 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. At present, the Longitudinal Optic Neuritis Study (LONS), which follows patients originally enrolled in ONTT, is underway. Taken together, these studies have provided well-established guidelines for treating optic neuritis and established an association between optic neuritis and multiple sclerosis. 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. However, results from LONS demonstrate that this latter treatment, although accelerating visual recovery, provided no long-term benefit to vision, and not treating is a viable option. Based on data collected from two 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 in the short term. The results from this research offered the first scientific evidence that intravenous corticosteroids help to delay the short-term progression of multiple sclerosis. However, long-term followup provided by LONS revealed the effect of corticosteroids in reducing the rate of development of multiple sclerosis was diminished after three years of followup. This study also demonstrated that the presence of multiple enhancing lesions on the brain MRI scan performed at the time optic neuritis was diagnosed was the single most important predictor of the development of multiple sclerosis within five years, and confirmation of these results was provided by LONS. LONS investigators are currently conducting a 15-year followup of enrolled patients.

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 (e.g., Sjögren's syndrome) but also occurs in association with aging, nerve dysfunction, radiation therapy, and antidepressant and antipsychotic drug therapy.

Lacrimal insufficiencies affect roughly two million Americans, particularly postmenopausal women. 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. Primary Sjögren's syndrome is now defined as a systemic autoimmune disorder with a population prevalence of about 0.5 percent that differentially affects women (female-to-male ratio of nine to one).

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 people reach their 50s and 60s.

The corneal endothelium is a layer of cells that 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 tears 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 therapeutic factors to the eyes of patients with the disease.

Keratoconus

Keratoconus arises 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. Keratoconous has become better understood though investigations into the genetic predisposition of the disease, detection of early forms of the disorder through computerized topographic analysis, and advances in understanding the enzymology that underlies corneal thinning. Microarray technology is proving to be 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 an 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 was collected to characterize the disease across its course and to identify risk and protective factors that determine the severity and progression of the disease. Study findings demonstrate an association between corneal scarring and decreased vision in keratoconus. A causal contribution of contact lenses to corneal scarring was found, thus suggesting that modifying lens fit can reduce this risk factor. Investigators are continuing to analyze the data.

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 U.S. The incidence of AMD continues to rise as the population ages. Women have a 50 percent greater risk for AMD than men.

The macula is a specialized region near the center of the retina responsible for the 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 and their products and then determining 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 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. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and

other studies suggested that lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids might also have benefit in AMD and cataract. A second study, AREDS 2, is currently underway to test this hypothesis. A multicentered clinical trial, The Complications of Age-related Macular Degeneration Prevention Trial, assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision. Another study, Late Macular Degeneration in Older Women, aims to determine the incidence and progression of AMD in women over 80 years old as well as to identify factors associated with it, such as diabetes and cataract surgery.

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 among women than men. These include:

- **Optic Neuritis**
  Research priorities include research to develop an animal model of this disease to better understand the pathogenesis of the disorder, to develop immunomodulating therapies limiting 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

Functional tests used to measure vision loss due to glaucoma can be affected by estrogen. In addition, 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, it is unclear whether its 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 carotenoids in preventing the development of age-related macular degeneration and cataract.

The NEI is working with the NIDCR and the ORWH to enhance research opportunities in the diagnosis, epidemiology, and treatment of Sjögren's syndrome.

- **International Sjögren's Syndrome Registry**
  The NEI is co-funding an 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 University of California, San Francisco, and multiple international sites (e.g., U.S., Argentina, China, Denmark, Japan, and United Kingdom) have been established. There is plan to add India as a site pending approval of the Indian government. Sites have started accruing patients, which involves the use of the standardized "Baseline Eye Exam Form" and a "Baseline Eye Exam Standard Operating Procedures" developed by the consortium.
- **Sjögren's Syndrome: A Model Complex Disease**
  The NEI partnered with NIDCR in the issuance of an RFA titled Sjögren's Syndrome: A Model Complex Disease. The focus of this initiative is to promote a multidisciplinary approach to the study of the pathophysiology of Sjögren's syndrome. The objective is to define predisposing genetic and environmental factors, develop animal models, characterize the role of immunological components, and identify biomarkers. (RFA-DE-06-004)

National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases and to enhance the health of all individuals so that they can live longer and more fulfilling lives. To achieve this vision, the NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and government agencies. The NHLBI collaborates with patients, families, health care professionals, scientists, professional societies, patient-advocacy groups, community organizations, and the media to maximize the use of research results and leverage resources to address the public health needs of the nation. All activities of the NHLBI are carried out in a spirit of public service and with a commitment to excellence, innovation, integrity, respect, compassion, and open communication.

The NHLBI places high priority on improving the cardiovascular health of women by supporting fundamental and clinical research to elucidate the role of sex hormones in cardiovascular health, identify and enhance healthy behaviors, and develop methods and practices for prevention, diagnosis, and treatment. Its research programs have generated important new knowledge about the influences of lifestyle, menopause, chest pain, hypertension, diabetes, and drug treatment (including hormone therapy) in women and also have led to improved diagnostic tests and treatment guidelines for women. In particular, the NIH Women's Heath Initiative (WHI), which is administered by the NHLBI, and the NHLBI Women's Ischemia Syndrome Evaluation have yielded invaluable scientific advances. The former continues to provide sex-specific data regarding women's cardiovascular health, cancer, and osteoporosis and is now making available its rich resources to seed new investigations that address women's health needs. The latter is nearing completion of its second project period and plans to compete for additional funding to test and validate innovative diagnostic tools and further explore the pathophysiology of chest pain and non-obstructive coronary ischemia, a condition prevalent in women. *The Heart Truth*, the NHLBI national awareness campaign for women about heart disease, continues to flourish, extending the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease. The NHLBI Center for the Application of Research Discoveries, formerly the Office of Prevention, Education, and Control, has responsibility for *The Heart Truth*.

Accomplishments

Women's Health Initiative (WHI) Overview

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 FY 1998. More than 160,000 women from across the U.S., who were between 50 and 79 years of age at the time of their recruitment, enrolled in the WHI clinical trials and observational study, almost 30,000 of them are minorities. The clinical trial component, now completed, 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 factures 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 CDC to examine strategies for enhancing the adoption of healthy behaviors, particularly among minority and underserved women.

Although the active phases of the clinical trials have concluded, the WHI cohorts are the subject of considerable further research efforts. Participants in all of the WHI clinical trials of hormone therapy, low-fat diet, and calcium and vitamin D supplementation, as well as participants in the observational study, have been invited to join the WHI Extension Study, which will run through 2010. A time schedule has been established for appropriate release of the WHI data to qualified investigators. The NHLBI solicited proposals to conduct additional research on a large biologic specimen repository collected through the WHI, including studies that link genetic information with clinical characteristics and outcomes. The first set of awards under this program will be made in January 2007, and the next are planned for 2008.

WHI Hormone Trials

The WHI postmenopausal hormone trials 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.

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.

In March 2004, the second hormone trial component also was halted ahead of schedule. With an average of nearly seven years of followup completed, the trial revealed that estrogen-alone therapy had no effect on CHD risk, but it increased risk of stroke and blood clots in the legs. 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. Results reported during FY 2005-2006 include the following:

Effect of Estrogen-alone Therapy on Risk of Stroke

As noted above, the estrogen-alone trial was stopped early primarily because treatment was associated with an adverse effect on risk of stroke. WHI scientists found that estrogen given by itself caused a significant increase in ischemic stroke (a blockage of blood flow to the brain), though not hemorrhagic stroke (a leakage of blood into part of the brain). A subsequent, more detailed analysis revealed that among every 10,000 women studied, 38 in the estrogen-alone group compared with 25 in the placebo group experienced an ischemic stroke each year. Analysis of subgroups of women according to their race/ethnicity, age, smoking status, hypertension status, or prior cardiovascular disease did not uncover

any variations in risk of stroke. The similarity between these results and those from the previously reported estrogen-plus-progestin trial strengthens the conclusion that a decision to prescribe or use estrogen therapy should consider the risk of stroke along with other known risks and benefits of taking estrogen. (Hendrix, S.L., et al. *Circulation* 113:2425-2434, 2006)

Effect of Estrogen-alone Therapy on Breast Cancer and Mammography Screening

Women enrolled in the WHI hormone trials received mammography screenings and clinical breast examinations at baseline and annually thereafter. In contrast to the estrogen-plus-progestin trial, which found higher rates of breast cancer among women assigned to hormone treatment, data at the time the estrogen-alone trial was halted revealed no harm with regard to breast cancer—and, in fact, suggested a slight benefit. A subsequent analysis examined this issue more closely. After an average of 7.1 years of followup, participants in the estrogen group had a 20 percent lower risk of invasive breast cancer than those in the placebo group. The difference between the groups was not statistically significant, but the data provide some reassurance that breast cancer risk is not increased for at least seven years among postmenopausal women who have had a hysterectomy and are taking estrogen. The women in the hormone group did, however, have significantly more abnormal mammograms and needed more breast biopsies, an outcome that must be taken into account when weighing the pluses and minuses of hormone therapy for a given individual. (Stefanik, M.L., et al. *Journal of the American Medical Association* 295:1647-1657, 2006)

Risk of Venous Thrombosis (VT) among Users of Postmenopausal Hormone Therapy

A number of observational studies have found an association between postmenopausal hormone therapy and increased risk of VT, including deep vein thrombosis (blood clots in the legs) and pulmonary embolism (blood clots in the lungs). The WHI hormone trials produced evidence consistent with these findings. Estrogen-plus-progestin therapy doubled the risk of VT and added to the known risks associated with age, overweight or obesity, and factor V Leiden, a genetic disorder that predisposes to VT. Moreover, regular use of aspirin did not protect trial participants on active hormones from developing venous blood clots. The estrogen-alone trial also found an increased risk of VT in women assigned to take the hormone, especially during the first two years, although the risk elevation was less than that for women in the WHI taking estrogen plus progestin. The WHI results reinforce the recommendation that women should use hormone therapy only after careful consideration of risks and benefits, especially if they have other risk factors for VT. (Smith, N.L., et al. *Journal of the American Medical Association* 292:1581-1587, 2004; Curb, J.D., et al. *Archives of Internal Medicine* 166:772-780, 2006)

Effects of Hormone Therapy on Urinary Incontinence (UI)

Although postmenopausal estrogen therapy has been thought to be useful for women with UI, the WHI trials found evidence to the contrary. Women who did not have UI when they joined the trials had an increased risk of developing it after one year if they were in the active rather than the placebo group. This risk was 39 percent higher for women taking active hormones in the estrogen-plus-progestin trial and 52 percent higher for such women in the estrogen-alone trial. Among the various types of UI, the risk was highest for developing stress incontinence. Among women who reported some UI when they joined the WHI, estrogen with or without progestin worsened both the frequency and amount of UI after one year when compared with placebo. In addition, women taking the active hormones were more likely to report that the UI bothered them and that it limited their daily activities. (Hendrix, S.L., et al. *Journal of the American Medical Association* 293:935-948, 2005)

Effects of Estrogen-alone Therapy on Health-related Quality of Life

The WHI investigators collected information on a variety of health-related quality-of-life measures at the beginning of the trial as well as one and three years afterward. They found that women assigned to take estrogen alone experienced a small reduction in sleep

disturbances and a small decrement in social functioning one year after the start of the trial. However, these women did not have any significant changes in general health, physical functioning, pain, vitality, role functioning, mental health, depressive symptoms, cognitive function, or sexual satisfaction at year one. Moreover, a subgroup examined at year three had no significant changes in any measures of health-related quality of life. These results are consistent with findings previously reported from the estrogen-plus-progestin trial and indicate that postmenopausal hormone therapy does not confer any quality-of-life benefit for the general postmenopausal population. (Brunner, R.L., et al. *Archives of Internal Medicine* 165:1976-1986, 2005)

Other Topics

WHI hormone trial findings also were reported for the following topics:

- Dementia, mild cognitive impairment, global cognitive function (Espeland, M.A., et al. *Journal of the American Medical Association* 291:3005-3007, 2004)
- Diabetes (Seaquist, E.R. *Diabetologia* 47:1133-1134, 2004)
- Gallbladder disease (Cirillo, D.J., et al. *Journal of the American Medical Association* 293:330-339, 2005)
- Symptom experience after discontinuing hormone therapy (*Journal of the American Medical Association*, July 13, 2005)
- CHD (Mackey, R.H., et al. *Archives of Internal Medicine* 165:510-515, 2005)

WHI Dietary Modification Trial

Results of the WHI Dietary Modification Trial were reported in February 2006. The 48,835 women who participated in the trial were randomly assigned to follow a special dietary plan or to continue their normal eating patterns. Women in the dietary change group were asked to decrease their fat intake to 20 percent of total daily calories, increase fruits and vegetables combined to five or more servings per day, and increase grains to six or more servings per day. During the course of the trial, the women approached but did not achieve these goals. After an average followup of 8.1 years, the study found no significant differences in the rates of colorectal cancer, CHD, or stroke between the dietary change group and the comparison group. Although the women in the study who reduced their total fat intake had a 9 percent lower risk of breast cancer than women who made no dietary changes, the difference was not large enough to be statistically significant. Conceivably, with longer followup, a stronger trend may emerge. The lack of benefit for CVD outcomes may have occurred because the primary interest of the trial was breast cancer, and, therefore, the intervention focused on reducing total fat and did not differentiate between "good" fats found in fish, nuts, and vegetable oils and "bad" fats, such as saturated and trans fats. (Prentice, R.L., et al. *Journal of the American Medical Association* 295:629-642, 2006)

The trial also allayed concerns that the popularity of low-fat, high-carbohydrate diets in the U.S. may contribute to the current obesity epidemic. To the contrary, the study found that women in the dietary change group lost weight during the initial year of the trial and maintained lower weight than women in the comparison group throughout the followup period. It was concluded that following a low-fat diet does not promote weight gain in postmenopausal women.

WHI Calcium and Vitamin D Study

Results of the WHI Calcium and Vitamin D Study also were published in February 2006. The study recruited 36,282 participants from the other WHI clinical trials and randomly assigned them to take either a twice-daily calcium-vitamin D supplement or a placebo pill. The trial found that the supplements provided a modest benefit in preserving bone mass and prevented hip fractures in certain groups, including older women and women who took the full intended dose of the supplements over the seven-year duration of the study. However, they had no effect on other types of fractures. Moreover, the supplements produced no detectable effect on the incidence of colorectal cancer. Although generally well tolerated, the supplements were associated with an increase risk of kidney stones. (Jackson, R.D., et al. *New England Journal of Medicine* 354:699-683, 2006)

WHI Observational Study

The WHI Observational Study enrolled more than 93,000 postmenopausal women aged 50 to 79 years and followed them for an average of nine 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. Topics of study findings reported during FY 2005-2006 include the following:

- Cardiovascular disease (CVD) outcomes and antihypertensive drug treatment (Smith, N.L., et al. J*ournal of the American Medical Association* 292:1581-1587, 2004)
- Physical activity and diabetes risk (Hsia, J., et al. *American Journal of Preventive Medicine* 28:19-25, 2005)
- Fracture risk among breast cancer survivors (Chen, Z., et al. Archives of Internal Medicine 165:552-558, 2005)
- Leukocyte count and CVD risk (Margolis, K.L., et al. *Archives of Internal Medicine* 165:500-5008, 2005)
- Mortality, CVD, and extreme obesity (McTigue, K., et al. *Journal of the American Medical Association* 296:79-86, 2006)

Women's Ischemia Syndrome Evaluation (WISE) Study

The WISE is a multicenter study initiated by the NHLBI in 1996 to evaluate ischemic heart disease (IHD) in women. Its primary focus is on improving symptom assessment and diagnostic testing, understanding the biological mechanisms responsible for myocardial ischemia in the absence of epicardial coronary artery disease (CAD), and determining the influence of reproductive hormones on heart disease symptoms and responses to diagnostic tests. The WISE enrolled and studied more than 900 women who had symptoms of IHD (e.g., chest pain, shortness of breath) and were referred for diagnostic angiography. In FY 2001, the NHLBI extended followup of the WISE cohort 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. A special supplement to the *Journal of the American College of Cardiology* (February 7, 2006) on IHD in women included a number of papers from the WISE, some of which are summarized below.

Insights from the WISE

The WISE has greatly increased understanding about IHD in women and about gender-specific symptoms, risk factors, and pathology. The study found that approximately 50 percent of its enrollees did not, in fact, have blockages in their large coronary arteries, yet many of them continued to experience debilitating symptoms or went on to have heart attacks. Microvascular dysfunction (impaired functioning of the small arteries of the heart, which is generally not detected by angiography) was often associated with the ischemia experienced by this large group of women. These findings indicate that CHD risk factors should be addressed aggressively in women with symptoms, even in the absence of a positive angiogram, and that better approaches to evaluate cardiac ischemia in women should be developed and used.

Potential Diagnostic Tool for Ischemic Heart Disease

The WISE used the Duke Activity Status Index (DASI) to estimate a woman's physical strength and ability to exercise. This simple, 12-item questionnaire inquired about everyday living and recreational activities, such as the ability to climb a flight of stairs or run a short distance. Investigators found that the DASI provided valid predictive information about a woman's future risk of suffering a heart attack or some other CVD manifestation. When the women were stratified into quartiles based on DASI-assessed physical capacity, the probability of surviving five years without suffering a heart attack fell progressively from 95 percent in the most robust group to 83 percent in the group with the greatest impairment in physical ability. Overall, 67 percent of all deaths or heart attacks occurred in women with the poorest DASI scores. Although validation in

other populations of women is needed, the DASI may prove useful as a regular part of a woman's diagnostic evaluation for IHD.

In another study, WISE investigators found a significant association between impaired physical capacity, as estimated by the DASI, and impaired coronary artery reactivity to adenosine, a vasodilator. Usually, when adenosine is injected into a coronary artery, the microvasculature dilates and coronary blood flow velocity increases, but this typical response was blunted in women with poor physical capability, even when age and the presence of CAD were taken into account. While the relationship between these two impairments needs clarification, the DASI shows promise as a useful indicator of CVD risk related to coronary vascular dysfunction.

Blood Pressure (BP) Levels and CAD Risk in Premenopausal Women

The WISE reported that the influence of BP on CAD development in women is, to some extent, a function of menopausal status. As a group, the study's premenopausal women had lower systolic BP levels. However, elevated systolic BP before menopause turned out to be a powerful CAD risk factor. Each increment of 10 mm Hg was associated with a 35 percent increase in CAD among premenopausal women, in contrast to 7 percent increase in postmenopausal women. The WISE data showed that high pulse pressure was also a significant risk factor for CAD in premenopausal but not in postmenopausal women. The results suggest that BP abnormalities in premenopausal women are serious signs of impending trouble and should alert physicians to the need for additional evaluation and close attention to risk-factor management.

Women's Health Study (WHS)

The WHS—a randomized, placebo-controlled clinical trial—evaluated the use of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) to prevent CVD and cancer. About 40,000 women who were 45 years of age or older were enrolled from 1992 to 1995 and followed for 10 years. In FY 2005, the WHS was extended for an additional five years to enable further evaluation of clinical issues related to CVD risk. Blood samples from more than 28,000 participants, which were frozen and stored at the beginning of the trial, are being made available for genetic analysis and other studies. This work is expected to improve prediction of CVD outcomes and of health conditions that are, by themselves, major CVD risk factors (i.e., type 2 diabetes, hypertension, metabolic syndrome); to evaluate genotype-phenotype interactions; and to shed light on interrelationships among multiple CVD risk factors in the prediction of CVD events. Recent findings from the WHS are described below.

Low-dose Aspirin and Vitamin E Supplements

The WHS found that low-dose aspirin and vitamin E supplements play a minor role, if any, in protecting women from CVD. Aspirin use did not prevent first heart attacks or CVD deaths. It did, however, reduce strokes by 17 percent in the overall study cohort and lower the risk of major CVD events by 26 percent among women who were 65 years of age or older. The study also showed that vitamin E supplementation had no effect on heart attacks, strokes, or total deaths, and—with regard to another hypothesized benefit—it did not reduce rates of breast, lung, colon, or other cancers. The NIH continues to recommend that women focus on other, well-proven approaches for reducing their risk of heart disease and stroke—eating a healthy diet; getting regular physical activity; maintaining a healthy weight; abstaining from smoking; and controlling high cholesterol, high blood pressure, and diabetes. (Ridker, P.M., et al. *New England Journal of Medicine* 352:1293-1304, 2005; Cook, N.R., et al. *Journal of the American Medical Association* 294:47-55, 2005)

C-reactive Protein (CRP) and CVD Risk

An analysis of data from more than 15,000 women in the WHS cohort has shed light on the value of high-sensitivity CRP measurement—an indicator of inflammation—in predicting risk of CVD. Researchers found that adding CRP to risk-prediction models based on traditional risk factors (i.e., age, cholesterol, blood pressure, smoking status, and use of hypertensive medication) improved the models' predictive accuracy, especially among women identified by the traditional models as being at intermediate risk. Furthermore, CRP's

relative contribution to overall CVD risk was at least as large as that due to total serum cholesterol, HDL cholesterol, or LDL cholesterol individually. The results suggest that incorporating CRP into CVD risk scores could in some cases improve CVD risk prediction. Moreover, the methods developed in the study may one day be useful for evaluating the utility of newly emerging biomarkers of inflammation in estimating CVD risk. (Cook, N.R., et al. *Annals of Internal Medicine* 154:21-29, 2006)

Exercise, Weight, and Biomarkers of CVD Risk

WHS investigators investigated the associations of physical activity and body mass index (BMI)—a measure of healthy body weight—with 11 biomarkers of CVD risk. They found that high BMI (i.e., overweight or obesity) conferred a greater risk of CVD than did low physical activity. However, overweight or obese women who exercised had better risk profiles than their inactive counterparts. The most favorable biomarker levels were found in women with optimal BMI who were moderately active as well. These results provide additional evidence of the importance of both weight control and physical activity for maintaining cardiovascular health. (Mora, S., et al. *Journal of the American Medical Association* 295:1412-1419, 2006)

Healthy Lifestyle and Risk of Stroke

Although much is known about the separate effects of various lifestyle factors on risk of stroke, the combined influence of such factors is unclear. The WHS provided a unique opportunity to assess this issue, using data collected from about 37,000 women when they entered the study. Investigators found that after 10 years of followup, a healthy composite of five lifestyle factors—abstinence from smoking, low BMI, moderate alcohol consumption, regular exercise, and a healthy diet—was associated with a significantly reduced overall risk of having a stroke of any type as well as reduced risk of having an ischemic stroke. (Kurth, T., et al. *Archives of Internal Medicine* 166:1403-1409, 2006)

Comparing Lipid Measures of CVD Risk

Although measures of total cholesterol, LDL cholesterol, and HDL cholesterol have been used successfully to screen patients for CVD risk, recent studies have suggested that measurement of other lipid elements (i.e., apolipoprotein AI and apolipoprotein B100) might enable even better risk prediction. Using WHS data, researchers identified two measures—non-HDL cholesterol and the ratio of total cholesterol to HDL cholesterol—that were at least as good as the apolipoprotein measures for predicting cardiovascular events. Because these values are easily calculated from traditional cholesterol profiles, the analysis indicates no reason for replacing standard lipid measures with other more complex ones for predicting risk of a first heart attack or stroke or for establishing the need for a revascularization procedure in otherwise healthy women. (Ridker, P.M., et al. *Journal of the American Medical Association* 294:326-333, 2005)

NHLBI Growth and Health Study (NGHS)

The NGHS was undertaken in 1987 to examine racial differences in the development of obesity and other CVD risk factors in a large cohort of adolescent girls. About equal numbers of black and white girls were enrolled in the study at nine to 10 years of age and examined annually for nine years. Investigators obtained anthropomorphic measurements; dietary information, including eating patterns and nutrient intake; lipid, lipoprotein, and apolipoprotein profiles; and information about physical activity, family socioeconomic status, and psychosocial factors. In 2002, the NGHS reported that both black and white girls experienced a steep decline in physical activity during adolescence, with the greatest decline occurring in black girls. By 16 or 17 years of age, 56 percent of black girls and 31 percent of white girls in the study reported having no regular leisure-time physical activity. Recent findings published by the NGHS investigators are described in the following:

Decline in Physical Activity and Weight Gain in Adolescence

New results indicate that sharp declines in physical activity among adolescent girls are directly associated with excessive weight gain. Researchers found that relatively inactive girls gained an average of 10 to 15 pounds more

than active girls over the period of observation. Only small differences in BMI (the equivalent of about four to five pounds) were noted between active and inactive girls at ages nine and 10, but the differences widened substantially over the next nine years, as did differences in skinfold thickness (a measure of body fat) and activity status. The NGHS results send a simple public health message—preventing the steep decline in physical activity that occurs among adolescent girls is a crucial step for maintaining a healthy weight. (Kimm, S.Y., et al. *The Lancet* 366:301-307, 2005)

Nutritional Studies

NGHS researchers found that both black girls and white girls ate fast food more often as they grew older, and that, at every age, black girls ate fast food more often than white girls. More frequent fast-food consumption was associated with greater intakes of calories and sodium and a higher proportion of calories consumed from fat for girls of either race. Another analysis showed that girls who ate cereal sometime during the day had better overall nutrition and lower BMIs, even after factors such as physical activity levels were taken into account. The NGHS findings further emphasize the importance healthy dietary habits in youth. (Schmidt, M., et al. The Archives of Pediatrics and Adolescent Medicine 159:626-631, 2005; Barton, B.A., et al. *Journal of the American Dietetic Association* 105:1383-1389, 2005)

Interventions to Increase Physical Activity and Decrease Weight Gain in Youth

We Can! (Ways to Enhance Children's Activity and Nutrition)

A national education program called We Can! was designed for parents and caregivers to help children eight to 13 years of age maintain a healthy weight. Developed by the NHLBI in collaboration with the NIDDK, the NICHD, and the NCI, We Can! provides resources and community-based programs that focus on behaviors to encourage healthy eating, increase physical activity, and reduce sedentary or "screen" time. Since We Can! was launched in June 2005, more than 125 communities in more than 34 states have implemented its programs. Additional information and We Can! materials can be obtained from the NHLBI Web site.

Community Trials

The Girls Health Enrichment Multisite Studies (GEMS), initiated in 1999, seeks to identify approaches to preventing excessive weight gain by black girls during adolescence. Several interventions addressing diet, physical activity, and psychosocial and familial influences were developed during the initial phase of the study. Two of the most promising ones are now being evaluated in randomized, controlled trials. One of them is an after-school dance intervention in community centers to increase physical activity coupled with a home-based intervention to reduce television-watching; the other is an intervention held in community centers to encourage girls and their parents/caregivers to engage in healthy eating (increasing consumption of fruits and vegetables and decreasing consumption of sweetened beverages) and physical activity.

The Trial of Activity for Adolescent Girls (TAAG), initiated in 2000, is testing the effectiveness of a school- and community-based intervention to prevent the declines in physical activity levels and cardiovascular fitness that so frequently occur among middle-school girls. The intervention provides skills-building, supportive environments, and opportunities for participating in physical activity during and outside of the school day. Thirty-six schools and many community agencies are participating.

Nurses' Health Studies

The Nurses' Health Study, begun in 1976 and supported by the NHLBI since 1980, and the Nurses' Health Study II, begun in 1989, are two of the largest prospective cohort studies ever undertaken to investigate risk factors for major chronic diseases in adult women. Several recent findings are described in the following.

BMI, Physical Activity Level, and Mortality in Women

Obesity has been shown to increase the risk of chronic disease and premature death, but the extent to which physical activity might mitigate this relationship has been unclear. New results

from the Nurses' Health Study suggest that while physical activity can reduce the health risk associated with obesity, even a high level of physical activity cannot completely eliminate it. Although active obese women in the study had a lower risk of dying than their inactive counterparts, their risk was still higher than that of inactive women who were lean. However, the results still support the importance of physical activity. Active women in each BMI category had a lower risk of death than women with the same BMI who were inactive; women who were both lean and physically active had the lowest risk of death of all of the participants. The results show that maintaining a healthy weight and being physically active are both important for reducing an adult woman's risk of serious medical problems. (Jacobs, D.R. and Pereira, M.A. *New England Journal of Medicine* 351:2753-2755, 2004)

Physical Exertion, Exercise, and Sudden Cardiac Death (SCD)

Although many studies show that regular physical activity has beneficial cardiovascular health effects, concern exists that exercise or physical exertion could trigger SCD. New results from the Nurses' Health Study may help allay such fears. Investigators found that the risk of SCD during exercise, although higher than the risk while resting, was extremely low and confined to women who did not exercise regularly. Women who exercised more than two hours per week had no higher risk of SCD while exercising than they did while resting. Furthermore, over the long-term, women who exercised regularly had a lower risk of SCD than women who did not exercise. The results suggest that moderate-to-vigorous physical activity does not pose a cardiac hazard for women and that regular exercise can lower a woman's overall risk of SCD. (Whang, W., et al. *Journal of the American Medical Association* 295:1399-1403, 2006)

Phobic Anxiety and Risk of CVD

Women with high levels of anxiety caused by phobias (e.g., claustrophobia, agoraphobia) may have an elevated risk of dying from certain forms of heart disease. Researchers found that women who scored high on the Crown-Crisp Index, which measures common symptoms of phobic anxiety, were more likely than others to suffer fatal CHD or SCD, although their risk for non-fatal heart attacks was unaffected. The researchers speculate that phobic anxiety might increase CHD risk by disrupting heart rhythm and also by increasing the likelihood of unhealthy behaviors, such as smoking and physical inactivity. The results suggest that improving the diagnosis and treatment of phobic anxiety in women might also improve their cardiovascular health. (Albert, C.M., et al. *Circulation* 111:480-487, 2005)

Folate Intake and Hypertension Risk

Consuming an adequate amount of folate may decrease a woman's chances of developing hypertension, according to a recent report. In both of the Nurses' Health Study cohorts, women who consumed at least 1,000 micrograms of folate daily had a lower risk of developing hypertension than women who consumed less than 200 micrograms. The beneficial effect of folate was most pronounced among younger women. Although the recommended daily allowance of folate currently is 400 micrograms per day, the study suggests that women, especially at younger ages, may derive additional benefits from increasing folate intake to 800 or 1,000 micrograms per day. (Forman, J.P., et al. *Journal of the American Medical Association* 293:320-329, 2005)

Reduced Sleep and Weight Gain

Recent findings suggest that lack of adequate sleep is associated with persistent weight gain in middle-aged women. Women whose nightly sleep averaged six hours or less at baseline gained more weight over the ensuing 16 years than did women who averaged seven hours a night. Furthermore, women who slept relatively little were at significantly greater risk of experiencing a major future weight gain and were more likely to become obese. These associations remained even after researchers adjusted for differences in physical activity and diet. Although further research is needed to clarify the mechanisms by which sleep duration may affect weight, the findings suggest that approaches that focus on getting adequate sleep may help middle-aged women limit future excess weight gain. (Patel, S.R., et al. *American Journal of Epidemiology* 164:947-955, 2006)

Women's Heart Disease Awareness Campaign

The Heart Truth, the NHLBI's national awareness campaign for women about heart disease, continues to flourish, extending the reach of campaign messages and promotion of the red dress as the national symbol for women and heart disease awareness, to millions of women. More than 350 locally sponsored Heart Truth events have taken place, and more than 1.3 billion media impressions have been achieved. First Lady Laura Bush participates in national and local events as The Heart Truth's ambassador.

The Heart Truth Road Show helps participants learn about heart disease risk factors, provides free health screenings, and disseminates educational materials. Between April and October of 2006, the Road Show reached thousands of women visiting shopping malls in Pittsburgh, Memphis, Washington, DC, and Jacksonville, FL—cities with large populations of women at high risk for heart disease. In April 2006, the campaign launched the Heart Truth Champions program to recruit health advocates and educators in local communities to increase awareness about women and heart disease. Since the start of The Heart Truth's Women of Color Initiative in early 2005, campaign messages have reached thousands of African American and Hispanic women throughout the U.S. National Wear Red Day—the first Friday in February—has become an annual event when Americans wear red clothing and accessories in recognition of the importance of heart disease in women. It is clear that The Heart Truth message has reached the public. Awareness of heart disease as the leading cause of death among American women increased from 34 percent in 2000 to 55 percent in 2005.

The Heart Truth is conducted in partnership with the American Heart Association, the DHHS OWH, WomenHeart (the National Coalition for Women with Heart Disease), and other organizations committed to the health and well-being of women.

Lymphangioleiomyomatosis (LAM)

NHLBI-supported basic research into the origins and growth of LAM cells is providing insights that may someday help control the disease. Investigators have identified proteins that promote the growth and movement of LAM cells and that also suggest an explanation for how LAM cells can metastasize among different organs, including the lung, kidney, and lymphatics. More is being learned about the role of estrogen and why LAM affects women almost exclusively.

NHLBI-funded scientists exploring the cellular pathways affected by genetic abnormalities in tuberous sclerosis complex (TSC) and LAM cells found that an essential protein for controlling cell size and growth was missing or misshaped. This finding led quickly to a potential target for treatment of LAM when it was discovered that sirolimus (rapamycin) mimics the function of the missing protein. A promising pilot study of sirolimus as a possible treatment for TSC and LAM, sponsored by the NCI through the Quick Trial Initiative, provided a basis for the development of a larger and more definitive multicenter trial under the auspices of the Rare Lung Diseases Consortium, which is supported by the NIH ORD and the NCRR. The protocol is currently in the final stages of approval. Additional therapeutic approaches will most likely be needed, however, because LAM cell lines derived from different individuals appear to vary in their sensitivity to sirolimus. This observation and the evolving concept that LAM behaves like a neoplasm suggest that multiple drug therapy will be the key to controlling the disease.

The NHLBI intramural program continues to support the collection, processing, and distribution of LAM tissue. The Institute also continues to co-fund the annual scientific conference organized by the LAM Foundation.

New Treatment Guidelines for Pregnant Women with Asthma

In 2005, the National Asthma Education and Prevention Program (NAEPP) issued the first guidelines in more than a decade for managing asthma during pregnancy. The report, which includes discussion of medications that were not available when the last guidelines were published, updates treatment recommendations for pregnant women with asthma based on a systematic review of data on the safety of asthma medications during pregnancy. Because poorly controlled asthma can lead to serious medical problems for a pregnant woman and her fetus, the NAEPP concluded

that it is safer for pregnant women to be treated with asthma medications than to experience asthma symptoms and exacerbations. In addition to addressing pharmacologic options for controlling mild, moderate, and severe asthma and emergency treatment for women experiencing acute asthma exacerbations, the report emphasizes the importance of controlling asthma symptoms by identifying and limiting exposure to asthma triggers. It also reminds health care providers that several conditions often associated with asthma (e.g., rhinitis, sinusitis, gastroesophageal reflux) are frequently more troublesome during pregnancy and that appropriate treatment of such conditions is an integral part of asthma management. The full report and a Quick Reference Guide, which was originally published in the Journal of Allergy and Clinical Immunology in January 2005, are available on the NHLBI Web site.

Guidelines for the Diagnosis, Evaluation, and Management of Von Willebrand Disease

The NHLBI, in consultation with the American Society of Hematology, formed a working group to examine the current science in the area of von Willebrand disease and to develop science-based clinical recommendations for its diagnosis, treatment, and management. The panel of experts completed their deliberations in 2006, and draft guidelines were made available for public review and comment. The recommendations are intended for practicing primary care physicians (e.g., general practitioners, family practitioners, internists, gynecologists, pediatricians) as well as hematologists. The guidelines are expected to be completed by early summer 2007 and will be disseminated electronically on the NHLBI Web site and as printed documents. Von Willebrand disease is the most common inherited bleeding disorder. It affects equal numbers of men and women, but is more likely to cause serious symptoms in women (e.g., heavy menstrual bleeding, prolonged bleeding after childbirth).

Initiatives

Request for Proposals (RFPs)

- **Hispanic Community Health Study**
  The NHLBI solicited proposals for a multicenter epidemiologic study to identify, recruit, examine, and followup community-based cohorts of adults, all of Hispanic origin, aged 18 to 74 years. The four cohorts are majority Cuban, Puerto Rican, Mexican American, and Central American. The study will measure a number of distinctive factors hypothesized to influence risk, including social, behavioral, occupational, and lifestyle factors, as well as acculturation. Measures of obesity, activity, diabetes, lung function, cognitive function, hearing, dental conditions, and CVD risk factors will also be included. (NHLBI-HC-06-01&02)

Request for Applications (RFAs)

- **The Obese and Diabetic Intrauterine Environment: Long-term Metabolic or Cardiovascular Consequences in the Offspring**
  The NHLBI, the NIDDK, and the NCI issued this grant solicitation to investigate the effects of maternal obesity and diabetes on mechanisms that could potentially contribute to obesity, cancer, or cardiovascular or metabolic disease in the offspring. Emerging evidence suggests that maternal overnutrition may have similar long-term metabolic consequences in the offspring as those seen with undernutrition. (RFA-DK-05-014)

Program Announcements (PAs)

- **Chronic Fatigue Syndrome: Pathophysiology and Treatment**
  The NIH ORWH issued this grant solicitation with the NHLBI and other NIH components to encourage research on the epidemiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome in diverse groups and across the life span. Applications were solicited that address gaps in understanding of the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mediators influenc-

ing multiple body systems that are affected in this syndrome. (PA-05-030)

- **Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases**
  The NHLBI issued this grant solicitation (a re-announcement of PA-04-071) with other NIH components to stimulate research on the biology of the lymphatic system, to characterize the pathophysiologic mechanisms that cause lymphedema and lymphatic diseases, to develop new methods for quantifying 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 undergo surgery or radiation treatment for breast cancer.

Conferences and Workshops

- **NIH State-of-the-Science Conference on Management of Menopause-Related Symptoms**
  This conference was convened on March 21-23, 2005 and was co-sponsored by the NHLBI, the ORWH, and other entities within and outside of the NIH.
- **The Influence of Early Programming in the Development of Cardiovascular, Lung, Blood, and Sleep Disorders Working Group**
  September 27, 2005
- **The Intrauterine Environment: Long-term Consequences for Obesity and Metabolic Disorders Workshop**
  This workshop was convened on September 26-27, 2005 and was co-sponsored by the NHLBI and other NIH components.
- **WHI Conference: The WHI Legacy to Future Generations of Women**
  This conference was convened on February 28-March 1, 2006 and was co-sponsored by the NHLBI and the ORWH in collaboration with other NIH components.

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, MS 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.

During FY 2006, the NHLBI awarded contracts for the Hispanic Community Health Study, a long-term population study analogous to the JHS that will study Latinos. (See description under Request for Proposals).

Gender Analysis

As noted in the previous Accomplishments section, researchers recently identified a number of gender differences with regard to IHD pathology, symptoms, diagnosis, and response to treatment. The long-running Framingham Heart Study continues to yield comparisons of CVD risk in women and men, and the JHS and the new Hispanic Community Health Study are expected to be rich sources of data on gender differences.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

The National Human Genome Research Institute (NHGRI) led the 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 it has already begun to change the way we address research on women's health.

In October 2005, a different international consortium of dedicated scientists from six countries, again led by the NHGRI, announced

the production of a very different map of the human genome, one that may prove even more powerful because of its medical applications. The result is the "HapMap." Like the earlier sequence, all of the data from the HapMap has been placed in the public domain. The HPG spelled out the letters of the DNA code that all human beings share. The HapMap provides detailed information about the variation in the genome. The HapMap investigates those spelling differences in the human instruction book that predispose some people to different types of cancer as well as other diseases. In December 2006, the NHGRI awarded a contract to continue the HapMap Project to make it an even more powerful tool to reveal the way in which genetic variation is organized into chromosomal neighborhoods. As this information unfolds, the NHGRI will continue to investigate diseases specific to women.

In 1994, NHGRI investigators were among the first to report that women carrying the gene mutations called Breast Cancer 1 (BRCA1) or Breast Cancer 2 (BRCA2) have a higher risk of developing both breast and ovarian cancer than women without such mutations. The NHGRI continues to investigate the role of these genes in breast and ovarian cancer, and this research has led to better screening and treatment of those with a family history of breast cancer. In hopes of expanding the usefulness of this research, the NHGRI also supports research that explores the effect of educating women of different ages and ethnic group about benefits of genetic screening in evaluating their risk of inherited diseases.

Accomplishments

Breast Cancer

The NHGRI is involved in several ongoing breast cancer studies. These studies explore various aspects of breast cancer research. One case-control study, which involves a collaboration with doctors in Finland, is examining the family-based linkage and searching for genes other than BRCA1 or BRCA2 that may explain familial aggregation in families without the mutation. A similar study is looking at large families in the U.S. with a history of breast cancer but without known mutations at either BRCA1 or BRCA2. These studies are looking for evidence of other genetic loci that may be involved in modifying lifetime risk and age at onset of breast cancer in women who are mutation carriers. In a paper published recently in Cancer Research, NHGRI investigators examined the prevalence and predictors of BRCA1 and BRCA2 mutations in 1,628 women with breast cancer and 674 women without breast cancer who participated in a multicenter, population-based, case-control study of black and white women between 35 and 64 years of age. Numerous familial and demographic factors, when examined individually, were significantly associated with BRCA1 and, to a lesser extent, BRCA2 carrier status. The results have provided the first prevalence estimates for BRCA1/BRCA2 in breast cancer cases among understudied racial and age groups. The findings also show key predictors of mutation carrier status for both white and black women. As a continuation of that study, the NHGRI is now engaged in a larger study aimed at determining the role of missense changes in the BRCA1 and BRCA2 genes and breast cancer susceptibility in African American women. Using a variety of statistical methods, investigators have developed a list of missense changes that they believe are likely to be associated with the disease. Investigators are now working to develop lab-based methods to test functionality. (Malone, K.E., et al. Cancer Research 66:8297-8308, 2006)

Ovarian Cancer

About one fifth of ovarian cancer cases are found at an early stage. Finding cancer early improves the chances that it can be treated successfully. Nine out of 10 women treated for early ovarian cancer will live longer than five years after the cancer is found. Unfortunately, there is no reliable test to identify this cancer at an early stage, but several large studies are in progress to address this problem. Currently, NHGRI researchers are engaged in the pilot phase of a collaborative project to identify locations that are important for the regulation of gene expression in ovarian cancers. By using sequencing to identify sites of abnormal methylation in promoter regions, this project hopes to determine which regulatory regions and which genes are factors in the occurrence

of ovarian cancer. Investigators at the NHGRI were among the first to report that women carrying BRCA1 or BRCA2 mutations have a higher risk for hereditary breast ovarian cancer (HBOC) syndrome. The NHGRI noticed a lack of studies regarding knowledge, attitudes, and behaviors related to cancer genetics among Hispanic women of different ethnic groups at increased risk for HBOC. In 2006, the NHGRI awarded a grant to better understand cultural differences that may affect utilization of BRCA1/BRCA2 testing for HBOC among three major U.S. Hispanic ethnic groups: Mexicans, Puerto Ricans, and Cubans. Study findings will serve as the basis for a larger intervention trial based in public health department settings to educate Hispanic women at increased risk for HBOC about genetic counseling and testing for HBOC and possibly other hereditary cancers.

Uterine Cancer

In an effort to learn about the influence of genetic education, counseling, and the option of genetic testing on psychological and behavioral outcomes in individuals at risk for inherited diseases, researchers at the NHGRI are studying a particular form of hereditary cancer called hereditary nonpolyposis colorectal cancer (HNPCC). People who have HNPCC are at risk for many cancers, not just colon cancer. Women in these families have as high a risk of developing uterine cancer as they have of colon cancer. This research explores how patients perceive their risk of developing cancer and monitors the influence of education and counseling on mood, behavior, and family relationships.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases (NIAID) funds basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses that affect the health of women and girls. The NIAID involves women in many of its clinical studies on the treatment and prevention of autoimmune diseases, HIV and AIDS, and sexually transmitted infections (STIs). The NIAID also collaborates with other organizations on research initiatives aimed at improving women's health.

This report provides an overview of NIAID's recent accomplishments and initiatives in women's health research. These accomplishments include the expansion of the Autoimmunity Centers of Excellence, the Immune Tolerance Network, and the Autoimmune Disease Prevention Centers; the Phase II/III PRO 2000/5 Gel and Buffer Gel microbicide trials; the sequencing of the Trichomonas vaginalis genome; and the Phase III clinical efficacy trial of an investigational vaccine for genital herpes, known as the Herpevac Trial for Women. Other initiatives and programs covered in this summary include the Women's Interagency HIV Study (WIHS), the Centers for AIDS Research's (CFAR) Women's Health Supplement, the Microbicides Trials Network, and the HIV Prevention Trial Network conducted in the U.S. and overseas.

Accomplishments

Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome (HIV/AIDS)

Worldwide, women face the greatest risk of acquiring HIV due to substantial mucosal exposure to seminal fluids, prevalence of non-consensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. The number of women with HIV infection and AIDS has been increasing steadily worldwide.

In addition to the complications of AIDS that afflict men, infected women also suffer gender-specific manifestations of HIV disease, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, gender-specific abnormalities related to infection with human papillomavirus, as well as vulvar and vaginal carcinomas. Drug metabolism has also been shown to differ in women when compared with men, potentially resulting in differential responses to antiretroviral therapy and an increased incidence of drug toxicities in women.

Frequently, women with HIV infections have difficulty accessing health care and carry a large burden of caring for children and other family members who may also be HIV-infected. They often lack social support and face other challenges that may interfere with their ability to adhere to treatment regimens.

The NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives, including intramural studies, unsolicited research on women and HIV/AIDS, as well as the WIHS, a long-term cohort study, the CFAR women's health supplement, and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. These clinical trials are being conducted by the Microbicides Trials Network, the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Community Programs for Clinical Research on AIDS.

Epidemiologic Research

The NIAID supports epidemiological research on:

- the long-term natural and treated history of HIV infection in women, particularly research that evaluates the impact of antiretroviral therapy (ART) on the clinical course of HIV disease;
- the effect of hormonal, endocrine, and local factors on viral load and sexual transmission;
- older populations of HIV-infected women to investigate what pathogenic processes are related HIV, ART, and/or the aging process;
- the characterization of acute clinical events and concomitant infections and their impact on HIV disease progression; and
- the female genital tract compartment, including the microenvironment, HIV virology, and immunology of the female genital tract as compared to blood.

Women's Interagency HIV Study

The NIAID supports researchers who study the unique features of HIV/AIDS in women through the WIHS. The WIHS is the largest observational study of HIV-infected women in the U.S. The majority of the women who participate in the study are African American and Latina women living in urban areas. This study has yielded many important results that have led to a better understanding of how HIV is spread, how the disease progresses, and how it can best be treated. The Women and Infant Transmission Study (WITS), a large cohort study that was funded by the NIAID, is being phased out. The NICHD will support a long-term followup to that study.

Association of Cigarette Smoking with HIV Prognosis among Women in the Highly Active Antiretroviral Therapy (HAART) Era

Researchers analyzed data from the WIHS study to assess the association of cigarette smoking with the effectiveness of HAART among low-income minority women. Those women who participated in the study were followed for more than seven years and represented 72 percent of all women who initiated HAART between 1995 and 2003. After controlling for age, race, hepatitis C infection, illicit drug use, previous antiretroviral therapy, and AIDS acquisition during the pre-HAART era, researchers found that smokers on HAART had poorer viral responses and poorer immunologic responses than non-smokers. There was a greater risk of virologic rebound and more frequent immunologic failure observed among smokers. These findings indicate that some of the benefits of HAART are negated in HIV-infected women who smoke cigarettes. (Feldman, J.G., et al. American Journal of Public Health 96:1060-1065, 2006)

Prevention Research

Topical Microbicides

Current global estimates of people infected with HIV exceed 38 million, with the majority of these infections in women. In Africa, the proportion of women infected with HIV has exceeded 50 percent, and the most at-risk women appear to be those in marriages with partners who engage in sex outside of marriage. Thus, there is an intensified need for the development of a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. A topical microbicide is a prepa-

ration (e.g., gel, cream, film, or foam) that is applied to the vagina or rectum to inactivate or inhibit sexually transmitted pathogens, including HIV, that are being transmitted by either sexual partner. It is believed that topical microbicides might be more effective than condoms in preventing HIV infection because they would be easier to use and women would not have to negotiate their use, as they must often do with condoms. Microbicides may also provide protection to men who have sex with men and women. The ideal microbicide would be safe and nonirritating to the mucosal tissues, even if used on multiple occasions in a short period of time. In addition, they would be inexpensive, unobtrusive, both fast and longacting, easy to store, and appealing to potential users. Topical microbicides should be available in both spermicidal and nonspermicidal formulations so women would not have to put themselves at risk for acquiring HIV and other STIs in order to conceive a child.

NIAID-sponsored research supports the development of a topical microbicide that:

- prevents infection and/or viral replication by both cellfree infectious HIV particles and cellassociated infectious particles;
- is safe and noninflammatory (i.e., causes no irritation to the vaginal/cervical/urethral/rectal epithelium); and
- reduces transmission and acquisition of infection, including potentiation of HIV acquisition by other STIs.

Protection of Monkeys from Vaginal SHIV Challenge by Combinations of Vaginally Delivered Inhibitors of Virus-Cell Fusion

Taking three microbicides that target HIV cell entry targets, researchers showed that although each of the three molecules individually displayed some level of protection from infection, combinations of two or all three microbicide candidates were more effective at preventing vaginal transmission of SHIV in monkeys. This work has provided the first in vivo proof that combination microbicides can be more effective than individual microbicides. (Veazey, R.S., et al. *Nature* 438:9-102, 2005)

Bioengineering Lactobacilli to Secrete the HIV Inhibitory Protein Cyanovirin-N

Cyanovirin-N (CVN) is a protein purified from extracts of the cyanobacterium (blue-green alga) Nostoc ellipsosporum. In vitro and in vivo studies have shown CVN to be a highly potent inhibitor of HIV replication and transmission. One method that addresses barriers to deployment of a protein-based microbicide is bioengineering of naturally occurring Lactobacilli to act as a carrier, production, and delivery system. The CVN secreted by bioengineered Lactobacilli were found to maintain CVN's inhibitory properties. These studies have significantly expanded the scope of bioengineered Lactobacilli as a producer and delivery system for microbicides. (Pusch, O., et al. *Journal of Acquired Immune Deficiency Syndromes* 40:512-520, 2005)

Use of Frozen Cervical Tissues for Microbicide Testing in Cervical Explant Assays

The cervical explant (tissue moved from its original site and transferred to artificial medium for growth) tissue-based ex vivo organ culture method has become an important assay for assessing the potential efficacy and toxicity of candidate microbicides. Work by NIAID-sponsored researchers has shown that cervical tissues can be frozen and then used after thawing for assessing microbicide efficacy and safety. The ability to use frozen cervical tissues without significant loss of tissue integrity or susceptibility to HIV infection greatly increases the utility and potential availability of these tissues for microbicide studies by allowing collection and storage of tissues for future use. (Gupta, P., et al. *AIDS Research and Human Retroviruses* 22:419-424, 2006)

Prevention Research: Clinical Trials

Microbicide Trial Network

As part of the newly restructured HIV/AIDS clinical trials networks, an award was made to Magee-Womens Research Institute to lead the Microbicide Trials Network (MTN). Using a drug development model, the MTN will develop a highly focused microbicide research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission.

Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5 Percent PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women

A clinical trial, titled Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5 Percent PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women, is ongoing. The primary objectives of this trial are to: (1) evaluate the safety of Buffer Gel and 0.5 percent PRO2000/5 Gel (P) when applied intravaginally by women at risk for sexually transmitted HIV infection; and (2) estimate the effectiveness of Buffer Gel and 0.5 percent PRO 2000/5 Gel (P) in preventing HIV infection among at-risk women. Approximately 3,220 women will take part in the study, 800 of whom will take part in the Phase II portion of the study. Enrollment in the Phase II portion of the study, conducted as an uninterrupted lead-in to the Phase IIb portion, has been completed. Enrollment in the Phase IIb portion is ongoing at sites in Philadelphia; Lilongwe and Blantyre, Malawi; Harare and Chitungwiza, Zimbabwe; Lusaka, Zambia; and Durban and Hlabisa, South Africa. Further information on this study is available online at www.hptn.org/research_studies/hptn035.asp.

Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1 Percent Tenofovir Gel

A clinical trial, titled Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1 Percent Tenofovir Gel, was initiated in New York City; Birmingham, AL; and Pune, India. The primary objective of the study is to assess the safety of tenofovir gel for vaginal use in HIV-uninfected women vs. a placebo gel when used once daily or before intercourse. Further information on this study is available online at www.hptn.org/research_studies/hptn059.asp.

The Sexually Transmitted Infections Clinical Trials Group

The Sexually Transmitted Infections Clinical Trial Group (STI CTG) is preparing to initiate a Phase I trial to evaluate the safety of a twice daily, vaginally applied, microbicide gel. The proposed indication of this topical microbicide is the prevention of genital herpes. This microbicide is being tested in conjunction with the NIAID Division of AIDS (DAIDS) and with a proposed indication for prevention of HIV transmission. For additional information, please go online to www.fhi.org/stictg/index.htm.

HIV Microbicide Design and Development Teams

The milestonedriven program, titled HIV Microbicide Design and Development Teams, was awarded to Starpharma LTD. In the first year of funding, a clinical trial, titled A Phase 1, Placebo Controlled Study of the Safety of 3 Percent w/w SPL7013 Gel and Administered to the Penis of Healthy Male Volunteers Once Daily for Seven Days, was initiated at the Melbourne Sexual Health Clinic in Australia. In addition, other preclinical milestones for manufacturing and toxicity studies have been met.

HIV Prevention Preparedness Study

Accrual in the HIV Prevention Preparedness Study has been completed at four international sites in Zambia, South Africa, and Tanzania. The purpose of this study is 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. Data analysis and manuscript preparation are underway. Additional information about this study is available online at www.hptn.org/research_studies/hptn055.asp.

Prevention Research: Prevention of Mother-to-Child Transmission (MTCT) of HIV

Almost all HIV-infected children acquire the virus from their mothers before or during birth or through breastfeeding. In the U.S., approximately 25 percent of pregnant HIV-infected women not receiving antiretroviral therapy passed on the virus to their babies. The rate is significantly higher in developing countries. Most mother-to-child transmission, estimated to cause more than 90 percent of infections worldwide in infants and children, occurs late in pregnancy or during birth. Although the precise mechanisms are unknown, scientists think HIV may be transmitted when maternal blood enters the fetal circulation or by mucosal exposure to virus during labor and delivery.

The role of the placenta in maternal-fetal transmission is unclear and is the focus of ongoing research.

The risk of MTCT is significantly increased if the mother has advanced HIV disease, increased levels of HIV in her bloodstream, or fewer numbers of the immune system cells (CD4 + T cells) that are the main targets of HIV.

In general, in developing countries where safe alternatives to breastfeeding are not readily available, the benefits of breastfeeding in terms of decreased illness and death due to other infectious diseases greatly outweigh the potential risk of HIV transmission. In HIV-infected pregnant women, the safety and pharmacology of these potent drug combinations need to be better understood, and the NIAID is conducting studies in this area. NIAID-sponsored research on preventing MTCT focuses on:

- defining the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant, as well as risks for disease progression within the framework of clinical studies and trials;
- developing and testing additional antiretroviral strategies to prevent mother to infant HIV infection through clinical trials in the U.S. and international settings; and
- developing interventions for the prevention of HIV transmission via breast milk in settings where breastfeeding is the best assurance for infant nutrition.

Combining Preventing Maternal-to-Child Transmission with Active Case Finding for Tuberculosis

Tuberculosis (TB) is the preeminent manifestation of HIV infection and has become a leading cause of maternal mortality and morbidity in high HIV-prevalence settings. Active TB in pregnant women has potentially serious consequences for fetuses and newborns. In Soweto, South Africa, there is a more than 90 percent uptake of voluntary counseling and testing (VCT) for HIV during routine antenatal care, and almost one-third of pregnant women are HIV-infected. The posttest counseling session of the prevention of mother-to-child transmission program provides an opportunity to screen HIV-infected pregnant women for TB. In this study, 370 HIV-infected pregnant women were screened for symptoms of active TB by lay counselors at the posttest counseling session. If symptomatic, they were referred to nurses who investigated them further. Eight women were found to have previously undiagnosed, smear-negative, culture-confirmed TB. Researchers found that rates of TB in HIV-infected pregnant women are high, and screening for TB during routine antenatal care should be implemented in high HIV-prevalence settings. Active, undiagnosed TB is a clinically significant public health problem in HIV-infected pregnant women in Soweto. This study shows that symptomatic TB screening is feasible and should be considered for incorporation into routine antenatal VCT and clinical care of HIV/TB co-infected women and children. (Kali, P.B., et al. *Journal of Acquired Immune Deficiency Syndromes* 42:379-381, 2006)

The Centers for AIDS Research

The Centers for AIDS Research (CFAR) constitute a unique infrastructure program to support multidisciplinary, peer-reviewed AIDS research environments that coordinate studies, promote communication, provide shared services/expertise, and fund short-term feasibility studies that cannot be funded easily by other funding mechanisms. The CFAR program has supported a women's health research supplement that funded numerous pilot projects on women's health and AIDS research. Several accomplishments are listed as follows.

Tufts University and Brown University CFAR

This CFAR's women's health research supplement has helped establish an HIV and menopause clinic. The clinic aims to assemble a cohort of HIV-infected menopausal women that will help answer questions concerning osteoporosis/osteopenia and cardiovascular complications in the setting of HIV and menopause.

University of North Carolina, Chapel Hill CFAR

The HIV and Women's Health Working Group at the University of North Carolina, Chapel Hill CFAR is focused on aspects of HIV infection in women, including the role of family, domestic violence, poverty, menopause, gender roles, and other social conditions that surround

women with HIV. It also has a particular focus on the pharmacology of antiretroviral therapy in the genital tract of HIV-infected women. This group is in the process of opening a Women's Comprehensive Care Clinic with a research focus on increasing the recruitment, enrollment, and retention of women into HIV clinical trials.

CFAR MTCT Studies

Through pilot project awards and supplements funded through the CFAR developmental core, the following MTCT studies are underway:

- HIV risk factors and reduction of MTCT in Tomsk, Siberia;
- Efficacy of cognitive-behavioral interventions for HIV-infected mothers in South Africa; and
- Infant immunization to reduce pneumonia in HIV-positive women.

Sexually Transmitted Infections

The prevention and treatment of sexually transmitted infections (STIs) are critical global and national health priorities because of their devastating impact on women and infants and their interrelationships with HIV/AIDS. STIs and HIV are linked by both biological interactions and occurrence 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. 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, tubal or ectopic pregnancy, cervical cancer, and perinatal or congenital infections in infants born to infected mothers.

The NIAID supports research for more effective prevention and treatment approaches to control STIs, including:

- research to develop safe and effective vaccines, topical microbicides, therapeutics, and strategies for preventing and treating STIs and their sequelae;
- basic research on pathogenesis, immunity, and molecular and structural biology of sexually transmitted pathogens and the impact of STIs in various populations; and
- research to develop better and more rapid diagnostics.

Each year, an estimated 15 million Americans suffer the effects of STIs at a cost exceeding $16 billion. Recent studies indicate that the more prevalent STIs causing non-ulcerative diseases (i.e., chlamydia, gonorrhea, and trichomoniasis) as well as those causing ulcerative diseases (i.e., syphilis and chancroid) increase the risk of HIV transmission by at least two- to five-fold.

Because some infectious agents (e.g., Chlamydia trachomatis) can ascend to the upper female genital tract, the long-term consequences of infection are also more severe for women and may result in PID, infertility, or tubal or ectopic pregnancy. The harmful effects on babies born to infected mothers may include stillbirth, premature birth, and perinatal and congenital infections. Moreover, many infections are often asymptomatic in women, resulting in a delay or lack of treatment. Women and children bear a disproportionate burden of the harm caused by STIs. Group B streptococci (GBS) also cause infections in mothers during pregnancy as well as in the neonate. During pregnancy, women can be afflicted with amnionitis, endometritis, sepsis, and meningitis. Intrauterine infections from GBS can lead to stillbirth or sepsis. In addition, infants can also be infected with GBS during passage through the birth canal resulting in sepsis, pneumonia, and/or meningitis.

The NIAID supports a broad array of biomedical research focused on the STIs. Selected significant advances in sex- and gender-specific STI research are provided below.

Genital Herpes

There are two types of herpes simplex virus (HSV), and both can cause genital herpes. HSV type 1 (HSV-1) most commonly infects the lips, causing sores known as fever blisters or cold sores, but it also can infect the genital area and produce sores. HSV type 2 (HSV-2) is the usual cause of genital herpes, but it can also infect the mouth. HSV-2 is more common in women (approximately one out of four women) than in men (almost one out of five). Genital HSV infections can present serious health consequences, including lifelong

recurrent episodes of painful genital lesions, increased likelihood of HIV transmission and acquisition, and, for women, possible transmission to fetus or neonate that can result in neonatal brain damage or death.

The 1994-2004 CDC surveillance data showed the overall seroprevalence of HSV-2 to be 17 percent, which is a substantial decrease from the seroprevalence rate of 21 percent from 1988-1994. Decreases in HSV-2 seroprevalence were prominent among the 14- to19-year-old age group and continued through the young adult age group, even after adjusting for changes in sexual behavior. These promising data show that the trajectory of increasing HSV-2 from 988-1994 has been reversed. (Xu, F., et al. *The Journal of the American Medical Association*, 296:964-973, 2006)

The Herpevac Clinical Trial for Women is a pivotal phase III, double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. The study is enrolling 7,550 women at approximately 42 sites in the U.S. and Canada. This study is being conducted as a public private partnership with GlaxoSmithKline and the NIAID. More information on this trial is available at http://www.niaid.nih.gov/dmid/stds/herpevac.

Human Papillomaviruses

Human papillomaviruses (HPV) is the name of a group of viruses that includes more than 100 different strains. More than 30 of these viral strains are sexually transmitted, and they can infect the genital area of men and women. Most people who become infected with HPV will not have any symptoms and will clear the infection on their own. Some of the viral strains are called high-risk types and can lead to cancer of the cervix, vulva, vagina, anus, or penis, in addition to Pap test abnormalities. Low-risk types of HPV may cause mild Pap test abnormalities or genital warts.

HPV is of clinical and public health importance because persistent infection with certain oncogenic types can lead to cervical cancer. Cervical cancer is one of the most common cancers in women worldwide. On June 8, 2006, an HPV vaccine was licensed by the FDA for use in females between the ages nine and 26 years. Gardasil is the first vaccine developed to prevent cervical cancer, precancerous genital lesions, and genital warts due to HPV types 6, 11, 16, and 18.

Condom Use Reduces Risk of Genital HPV Infection in Young Women

NIAID-sponsored researchers evaluated whether the use of the male condom reduced the risk of male-to-female transmission of HPV infection. This study followed young women who reported their sexual activities just before and during the study period. Cervical and vulvovaginal samples for HPV DNA and Pap smears were collected, and sexual behavior was recorded in electronic diaries. Research results suggest the incidence of genital HPV was lower among women whose partners used condoms for all instances of intercourse when compared with those women whose partners used condoms less than 5 percent of the time. These findings suggest that among newly sexually active women, consistent condom use by their partners appears to reduce the risk of cervical and vulvovaginal HPV infection. (Winer, R.L., et al. *The New England Journal of Medicine* 354:2645-2654, 2006)

Chlamydia

Chlamydia trachomatis infections are among the most prevalent of all STIs. In women, chlamydial infections may result in PID, which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain. The rate of reported chlamydial infection is greater among women than men, and adolescent women are at the highest risk of infection. Asymptomatic infection is common in both men and women. In the U.S., the continued increase in reported chlamydia cases is likely to represent expansion of screening for the infection, the development of more sensitive screening tests, and more complete national reporting.

Chlamydia Protein Offers a Neutralizing Antigen

Chlamydia trachomatis is the leading cause of bacterial sexually transmitted disease and infectious preventable blindness. Despite decades of effort, there is no vaccine against C. trachomatis diseases. In this study, researchers conducted an investigation of a protein, polymorphic membrane protein D (PmpD), which was described decades ago as being found in multiple chlamydia strains. The results from

this study indicate that antibodies specific to this particular protein are neutralizing in vivo, but this action is blocked in vitro, suggesting that a decoy-like immune evasion strategy may be active in vivo. These results suggest a vaccine protocol using this recombinant protein (PmpD) to elicit neutralizing antibodies might offer protection from many or all strains of chlamydia and possibly surpass the level of protection achieved through natural immunity. This basic research may provide an important step toward the development of a vaccine against chlamydia infections. (Crane, D.D., et al. *Proceedings of the National Academy of Sciences of the United States of America* 103:1894-1899, 2006)

Chancroid

Chancroid is an acute ulcerative disease caused by Haemophilus ducreyi. It is endemic in many parts of the developing world and is an important risk factor for heterosexual spread of HIV. Chancroid usually occurs in discrete outbreaks in the U.S., although the disease is endemic in some areas.

Immunization with the Haemophilus ducreyi Hemoglobin Receptor HgbA Protects Against Infection in the Swine Model of Chancroid

The STI, chancroid, facilitates the spread of HIV in populations where both chancroid and AIDS are endemic. Thus, successful efforts to prevent chancroid may lower HIV infection rates in these populations. The etiologic agent of chancroid is Haemophilus ducreyi. Using a swine model of H. ducreyi infection, researchers demonstrated that an experimental HgbA vaccine prevents chancroid, as determined by several parameters, including histological examination and measurement of antibody activity. Anti-HgbA immunoglobulin G blocked hemoglobin binding to H. ducreyi's HgbA receptor, suggesting a novel mechanism of protection that works by limiting iron acquisition by the pathogen. This study provides the first example of a vaccine for chancroid with significant efficacy in an animal model. Taken together, these data support continuing the development of an HgbA vaccine to prevent chancroid. Such a vaccine strategy might also be applied to other bacterial pathogens with strict iron requirements. (Afonina, G., et al. *Infection and Immunity* 74:2224-2232, 2006)

Trichomoniasis

Trichomoniasis is a sexually transmitted infection that affects both men and women and results in approximately 7.4 million new cases in the U.S. Trichomoniasis infection commonly occurs in a woman's vagina, resulting in a vaginal discharge; vaginal odor; discomfort during sexual intercourse and urination; irritation and itching of the genital area; and, in rare cases, lower abdominal pain. Both men and women with trichomoniasis can have an increased susceptibility to HIV infection and may transmit HIV to their sexual partners. Pregnant women with the infection may deliver a low weight or premature infant. Although prescription drugs cure trichomoniasis, drug resistance has become an increasing concern.

Scientists Sequence Genome of Parasite Responsible for Trichomoniasis

NIAID-sponsored researchers have decoded the genetic makeup of the parasite that causes trichomoniasis, one of the most common STIs, revealing potential clues as to why the parasite has become increasingly drug resistant. This research suggests possible pathways for new treatments, diagnostics, and a potential vaccine strategy. (Carlton, J.M., et al. *Science* 315:207-212, 2007)

Immunology and Immune-mediated Diseases

The immune system is important at all stages of life in fighting disease-causing micro-organisms or pathogens, including viruses, bacteria, fungi, and parasites. The immune system discriminates self from non-self; however, women are able to carry a fetus without rejection. This ability seems to be at odds with the fact that women also suffer much more commonly than men from autoimmune diseases, where the immune system attacks its own tissues. In addition, many of the autoimmune diseases are more common after the onset of puberty or in middle to late life, times of changes in the hormonal environment in women. Pregnancy may exacerbate or ameliorate several immunologic diseases, including autoimmune diseases and asthma and allergic

diseases. In addition, increased understanding of the mechanisms of natural maternal-fetal tolerance may allow the development of new strategies for the induction of clinical tolerance and autoimmune disease. The NIAID supports a number of investigations on immunology and immune-mediated diseases and their effect on women's health. Selected accomplishments are provided in the following.

Autoimmune Diseases: Lupus

Systemic lupus erythematosus (SLE), more commonly known as lupus, is an inflammation of the connective tissues in the body. Lupus can afflict every organ system and is nine time more common in women than men. Lupus affects black women three times more often than white women.

Study of Estrogen Effects on B cells in Lupus

Results from the SELENA Study (Safety of Estrogen in Lupus Erythematosus National Assessment) demonstrate that estrogen can exacerbate lupus. Researchers are investigating those lupus patients who develop multiple disease flare-ups while on estrogen in comparison to those lupus patients whose disease is not hormonally modulated. Researchers are analyzing B cell function after exposure to estrogen and are looking for polymorphisms in genes that are associated with susceptibility to estrogen-induced worsening of disease. Studies of this type may permit researchers to better identify lupus patients at risk for estrogen-induced disease flare-ups as well as to identify cellular pathways. (Petri, M., et al. *The New England Journal of Medicine* 353:2550-2558, 2005)

Germinal Center Exclusion of Autoreactive B cells is Defective in Lupus

Researchers have found that a failure of B cells to mount an immune response to a foreign substance is central to the pathogenesis of lupus. This failure on the part of B cells is referred to as B cell tolerance. The subversion of B cell tolerance is poorly understood because of difficulties associated in identifying relevant autoreactive B cells and in obtaining lymphoid tissue. Scientists used tonsil biopsies to circumvent this limitation because B cells found in these biopsies were found to be abnormally regulated in lupus patients. This faulty regulation was not shared in rheumatoid arthritis patients. This type of research represents the first comparative analysis of the fate of a specific autoreactive B cell in the human population. This study addresses an important question about the origin of autoantibodies in lupus patients, which are thought to be due to the production of pathological autoantibodies. The researchers demonstrated that autoreactive B cells in lupus patients do not stop at a specific developmental checkpoint but proliferate, mature, and secret pathogenic autoantibodies. Novel lupus therapies may focus on strengthening this checkpoint as a way to prevent lupus flare-ups. (Cappioni, A. 3rd, et al. *Journal of Clinical Investigations* 115:3205-3216, 2005)

Regulation of B Cell Tolerance by the Lupus Susceptibility Gene

In this study, researchers demonstrated that a protein, Ly108, which is found in immature B cells, is unable to cause cell death triggered by binding antigen. This impairs a mechanism that removes autoreactive B cells. It may be possible to design drugs that increase this protein's activity as a means to provide new drug therapies for lupus patients. (Kumar, K.R., et al. *Science* 312:1665-1669, 2006)

Autoimmune Diseases of the Ovaries

Ovarian autoimmune disease is associated with premature menopause and is linked to unexplained infertility. Although some cases of premature menopause have a genetic basis or are due to chemotherapy, studies suggest that half of all cases of premature menopause are due to an autoimmune attack on the ovaries. In addition, approximately half of all women with unexplained infertility have antibodies that react specifically with the ovaries.

Association of Unexplained Infertility with Gonadotropin and Ovarian Antibodies

Scientists have gathered compelling evidence for an autoimmune disease of the ovary. Ovarian autoimmunity may affect as many as one to two million women in the U.S. To determine the relationship between ovarian and gonadotropin autoantibodies and unexplained infertility, researchers analyzed the ovary-specific antibodies found in the

blood of patients with unexplained infertility and a comparison group from a blood bank. Patients with unexplained infertility had either no gonadotropin treatment or two or more gonadotropin cycles to induce ovulation. There was no significant difference in ovarian autoantibodies between women who were treated with gonadotropin and those women who did not receive the treatment. While gonadotropin autoantibodies were significantly more frequent in women who received the gonadotropin treatment, they were also present, to a lesser extent, in untreated infertile patients. The findings suggest that gonadotropin antibodies may represent a separate marker of ovarian autoimmunity in unexplained infertility. This type of research furthers the study of disease pathogenesis of ovarian autoimmunity and contributes to a better understanding of an autoimmune disease that affects women's health. (Shatavi, S.V., et al. *American Journal of Reproductive Immunology* 56:286-291, 2006)

Autoimmune Diseases: Clinical Trials

The NIAID is supporting three clinical trials in stem cell transplantation to evaluate autologous hematopoietic stem cell transplantation for the treatment of three autoimmune diseases: scleroderma, systemic lupus erythematosus, and multiple sclerosis. These complex trials, which opened in FY 2006, will also include studies of the underlying immune mechanisms of these diseases and treatments.

Asthma and Allergies

The latest statistics show that asthma is on the rise. According to the CDC, more than 20 million Americans currently have asthma, and another 10 million have been diagnosed with asthma at some point in their life. Roughly 6.5 million American children, or nearly 9 percent of the nation's pre-adult population, have asthma. NIAID-sponsored researchers are investigating immune responses to asthma and other allergic conditions.

IL-1R Antagonist Gene and Prenatal Smoke Exposure Are Associated with Childhood Asthma

To gain a greater understanding of the mechanism for allergic asthma and other allergic diseases, researchers conducted genetic association studies using DNA from children with and without allergic diseases. In addition, researchers measured interactions between genes and smoking using the interleukin-1 receptor antagonist (IL-1R) gene polymorphisms to identify risk for pediatric asthma and bronchial hyperresponsiveness. In the analysis, the IL-1R gene was not found to be associated with asthma. However, in the stratum of maternal smoking during pregnancy, the genotype significantly increased the relative risk of asthma in children, both in repeated asthma occurrences and persistent asthma. Researchers found that in the first decade of life, the gene-environment interaction of the IL-1R gene and maternal smoking during pregnancy increased the risk of childhood asthma. (Ramadas, R.A., et al. *The European Respiratory Journal* 28:502-508, 2007)

Preventing Immune-mediated Pregnancy Complications

Pregnancy constitutes a major challenge to a mother's immune system because it requires tolerance of antigens encoded by the prospective father's genes. Failure of immune tolerance is a possible cause for recurrent miscarriages, high mortality and morbidity rates at birth, as well as long-term development delay and metabolic disorders during adult life.

Using an antibody-independent mouse model of spontaneous miscarriage, researchers are exploring how the activation of the inflammatory system leads to defective placental development. These studies provide the first evidence linking complement activation to an angiogenic factor imbalance associated with placental dysfunction, thus opening the way to monitor levels of complement activation in the serum of pregnancy women as a tool to predict and prevent immune-mediated pregnancy complications. (Girardi, G., et al. *Journal of Experimental Medicine* 203:2165-2175, 2006)

Research on Immunity in the Female Reproductive Tract

A number of bacteria, fungi, viruses, and protozoa can infect reproductive tissues, resulting in varying degrees of pathology ranging from little discomfort to death. The female reproductive tract has evolved innate and adaptive immune mechanisms that protect from microbial infection, thereby reducing

infection and disease. Central to this protection are the epithelial cells that line the female reproductive tract. In the uterus, columnar epithelial cells provide a physical barrier to microbial infection. In addition, epithelial cells produce chemokines and cytokines that attract and activate innate immune cells and serve as a link to the adaptive immune system. Further, uterine epithelial cells serve as a conduit for secretory antibodies to enter the lumen and can present antigen to T cells. These protective mechanisms contribute to an environment in the uterus that is generally considered sterile, unlike the environment in the lower female reproductive tract. The uterine environment is in constant flux due to the concentration changes in sex hormones that occur in preparation for reproduction. The sex hormones, estrogen and progesterone, alter the local immune system to prepare for conception, influence how well the immune system will tolerate antigenic sperm and a semi-allogeneic fetus, and yet provide a network of protective immune mechanisms against microbial pathogens. Understanding how sex hormones influence uterine epithelial cell function will provide a basis for immune protection in the uterus.

Estrogen Effects on Immunity in the Female Reproductive Tract

Researchers examined the effects of sex hormones on immune-mediated responses of uterine epithelial cells. This study showed that estrogen inhibited the ability of uterine epithelial cells to respond to an inflammatory stimulus (IL-1) while progesterone had no effect. Estrogen limited the ability of uterine epithelial cells to produce antimicrobial peptides that protect the female reproductive tract from infection and also limited the production of chemotactic molecules that recruit immune cells to the site of infection. These results suggest that inflammatory responses may be reduced during ovulation and pregnancy. (Schaefer, T.M., et al. *Journal of Immunology* 175:6509-6516, 2005)

Related Accomplishments in Women's Health: Research Training and Career Development

Primary Caregiver Technical Assistance Supplements (PCTAS)

The NIAID recognizes that postdoctoral scientists with young children or ailing parents may encounter barriers to career advancement when faced with the challenges of balancing the demands of research activities and primary caregiver responsibilities. As a result, productivity can be seriously compromised during this critical period of a young scientist's career. To support the career development of young investigators, the NIAID has created the PCTAS program to provide technical support to postdoctoral scientists who have primary caregiver responsibilities. Principal investigators with NIAID research grants are eligible to apply for technical support for a postdoctoral scientist for a period of one to two years. The program has been well received by the research community, and three awards were made in the past two years.

Strengthening International AIDS Research on Women and Children

Through an NIAID-sponsored grant on HIV research in women and children, the University of Washington CFAR provided funds to eight international sites in Kenya, Mozambique, and Peru, based on a peer-reviewed process, to strengthen these international sites conducting innovative HIV research on women and children. These include studies of mother-to-child transmission and HAART operational research, microbicide and prevention research, and vaginal infection research.

Mentoring International Investigators on HIV Research and Women's Health

A NIAID-sponsored grant at the Tufts University and Brown University CFAR has provided mentoring to international investigators on research related to HIV and women. Some of the services include hands on training in gynecological collection methods, STD diagnosis, advice on establishing an HIV and women clinics, preparation and submission of grants, and implementation, analysis, and publication of research on HIV-infected women. The

CFAR core also helps mentor Brown University students, residents, and fellows interested in international work related to HIV and women in South Africa, Kenya, Cambodia, the Philippines, and Cape Verde.

Trans-NIAID Women's Health Research Workgroup

In 2006, NIAID established a Trans-NIAID Women's Health Research Workgroup consisting of staff to advise the NIAID on matters pertaining to women and gender based research. The workgroup is focused on women's health and gender-based research activities that advance the mission and research priorities of the NIAID, identify any gaps in research, and provide recommendations for future women's health research opportunities. The programmatic goals of the workgroup are three-fold:

- to advise on the coordination of women and gender based research across the Institute;
- to develop a common framework for identifying and assessing women and gender based research; and
- to encourage trans-NIAID and trans-NIH collaborations on women and gender based research activities.

Initiatives

Request for Proposals (RFPs)

- **Specialized In Vitro Virological Evaluations of Strategies to Combat HIV/AIDS**
  The scope of the contract is to test compounds for their potential to be developed as topical microbicides in primary and secondary cell-based assays for their efficacy and safety.
- **STD Prevention Primate Unit**
  The STD Prevention Primate Unit for preclinical evaluation of topical microbicides and vaccines at the University of Washington is being recompeted. An award is anticipated in 2007. This contract will evaluate microbicide candidates for safety (e.g., effects on surface tissues and microenvironment of the cervix and vagina) in pigtailed macaques and for efficacy against STI pathogens. Results from this NIAID-supported testing contract are coordinated with other NIAID-funded testing to facilitate product development and safety and efficacy testing in clinical trials. (RFP-07-18)
- **Immune Tolerance Network (ITN)**
  This RFP supports the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the U.S., Canada, Europe, and Australia. The ITN is 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 "reeducate" 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. Since its inception, the ITN has initiated more than 20 clinical protocols, more than 15 state-of-the-art core laboratory facilities, and more than 10 additional studies designed to explore immune mechanisms leading to the development, maintenance, or loss of clinical tolerance. Currently, the ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts. The ITN is co-sponsored by the NIDDK and the Juvenile Diabetes Research Foundation International (JDRF). (RFP-AI-04-44) More information on the ITN is available on its Web site at www.immunetolerance.org.
- **The Multiple Autoimmune Diseases Genetics Consortium (MADGC)**
  This RFP resulted in the MADGC, a repository of genetic and clinical data and specimens from families in which two or more

individuals are affected by two or more distinct autoimmune diseases. This repository provides well-characterized genetic material on 363 families for use in research aimed at identifying the genes involved in autoimmune diseases. Samples from 1,243 affected individuals and approximately 1,000 control subjects, all with associated clinical information, are available to qualified researchers. (RFP-AI-99-30)

Request for Applications (RFAs)

- **Microbicide Innovation Program (MIP)**
  The NIAID, in coordination with the NIH Office of AIDS Research (OAR), developed a new milestone-driven microbicide research program that was co-funded by the ORWH and co-sponsored by the NICHD and the NIMH. The focus of the RFA is to encourage: (1) the discovery and exploration of microbicides (singly or in combination) directed against HIV or HIV and STIs linked to HIV acquisition; (2) the study of emerging technologies or models that contribute to the development of new and/or more efficient methods of assessing microbicide safety, efficacy and acceptability; and (3) the exploration of complex prevention strategies that incorporate microbicides with other modalities of prevention. Fifteen applications were identified for funding, one by the NIMH, three applications by the NICHD, and 11 applications by the NIAID. (RFA-AI-06-005)
- **Partnerships for Topical Microbicides Program**
  In FY 2005, through this RFA, the NIAID made five awards that join together industry and academic or other non-profit organizations to develop and bring promising topical microbicide candidates from concept through pre-industry development to prepare them for clinical trials. The focus of these partnership agreements is to develop a potential microbicide with a proposed dual indication (i.e., prevention of HIV and an STI or prevention of two STIs). (RFA-AI-04-047)
- **Improving Diagnostics Associated with Women's Health and Sexually Transmitted Infections**
  In 2002, the NIAID established a program of research to stimulate industry participation in the development of vaccines, drugs, and diagnostics for human infectious diseases of public health importance and products for controlling vectors that transmit infectious agents. In 2005, the Partnerships to Develop Tools to Evaluate Women's Health was initiated to develop and evaluate a variety of tools and methods that will help define the complex ecosystem of the vaginal flora and pathogens in the context of immune response of the female reproductive tract. Specific areas of research include assessing the vaginal ecology, measuring immune responses in the vagina, and assessing the influence of reproductive hormones on the vaginal ecosystem and the immune responses. Research also includes investigating the women's reproductive tract in both normal and altered physiological conditions. During 2006, three companies were awarded grants through this partnership. They were the Mattek Corporation, which is investigating vaginal/cervical tissue models and endocrine effects and susceptibility to infection; the Institute for Genomics Research, which is developing genomic tools for studying the ecology of the human vaginal microflora; and the Program for Appropriate Technology for Health, which is developing a multiplex point-of-care test for vaginal infections. (RFA-AI-05-029)
- **Autoimmunity Centers of Excellence (ACEs)**
  This RFA resulted in nine ACEs to conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multisite 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. Clinical trials supported through the ACEs include: Phase I/II clinical trial of anti-CD20

for treatment for lupus; Phase I clinical trial of anti-TNF for treatment of lupus nephritis; Phase I clinical trial of anti-CD20 for treatment of Sjogren's syndrome; and preclinical study of DNase treatment, now underway with a follow-on phase 1b trial planned. Mechanistic studies supported through the ACEs include a study of immune responses against therapeutic anti-TNF molecules that could compromise their efficacy in rheumatoid arthritis, and an analysis of regulatory T cells induced in patients treated with anti-CD3. The ACEs are co-sponsored by the NIDDK and the NIH ORWH. (RFA-AI-05-026) Additional information on the ACE is available on its Web site at http://www.autoimmunitycenters.org.

- **The Autoimmune Disease Prevention Centers**
  This RFA support the Autoimmune Disease Prevention Centers, which 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 2005, the Prevention Centers supported 22 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. (RFA-AI-05-026)
- **Sex-based Differences in the Immune Response**
  The NIAID, in collaboration with the NIAMS, the NINDS, the ORWH, and the National Multiple Sclerosis Society, supports the Sex-based Differences in the Immune Response research initiative. In addition, the NIAID, with the NIH OAR and the 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. (RFA-01-005)

Program Announcements (PAs)

- **Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM)**
  This PA, which was co-sponsored with the NICHD, continued through 2006. The purpose of the PA is 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 as well as 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 topical microbicide network. Three new awards were made to the Harvard Medical School, the Population Council, and Brown University. They will expand significantly the scope of the IPCP-HTM by introducing programs focusing on development of microbicides for HIV, HSV, and HPV and preclinical development of a triple combination microbicide. In addition, previous awards were proposed for competitive supplements. The competitive supplements were targeted to add specific functionality to the existing IPCP-HTM awards through core funding. Two awards were made to University of California, Los Angeles and Starpharma, Ltd. to develop and clinically evaluate a form of the microbicide formulated for rectal use. (PA-03-137)

Conferences and Workshops

- **Workshop on Self-obtained Vaginal Swabs for Diagnostic Testing**
  A workshop was held in June 2006 in Bethesda, MD to present published data on self-obtained vaginal swabs for diagnostic testing. Representatives from the FDA, the CDC, and the NIH attended the workshop along with investigators and companies involved with in vitro diagnostics. Active dialogue among conference participants may lead to future collaborations.

- **Workshop on Regulation of Inflammatory Responses: Influence of Sex and Gender**
  On September 19-20, 2006, the NIH ORWH and the NIAID convened a workshop on the influence of sex and gender on the regulation of inflammatory responses. Investigators from the U.S. and Europe presented their research findings and provided participants with a state-of-the-science. Representatives from across the NIH attended the workshop, including representatives from the NCI, the NHLBI, the NIA, the NIAAA, the NIAMS, the NICHD, the NIDCR, the NIDA, the NIGMS, the NIMH, and the NINDS. The initial session provided a basic foundation of what inflammation is, and subsequent sessions explored sex differences in the burden of disease and response to insult, cellular and molecular mechanisms in inflammation, and emerging strategies to treat inflammatory disease. Presentations were followed by discussions in which workshop participants identified gaps in knowledge, research needs, and opportunities for future research. Recommendations for research opportunities will be incorporated into a trans-NIH initiative on inflammation.
- **Workshop on Development of Standardized Microbicide Toxicity Tables for Clinical Trials**
  NIAID staff organized a workshop titled Development of Standardized Microbicide Toxicity Tables for Clinical Trials. The toxicity tables will be used in NIH-sponsored vaginal and rectal microbicide trials, as well as those sponsored by other agencies. Participants included interested stakeholders from the NIH, the FDA, industry, and other funding agencies. The workshop was on held November 2-3, 2006 in the Washington, DC area.
- **World AIDS Day Conference on Women's Health**
  The Harvard University CFAR participated in the conference, World AIDS Day: Living our Lives - A World AIDS Day Conference on Women, which was held on December 1, 2005. This conference, which was held at University of Massachusetts-Boston, was organized by a multiagency planning committee and drew more than 150 attendees. The conference included a range of topics, such as sessions on domestic violence, addiction, and women's health concerns, as well as a vendor fair that provided resources and information to participants about local community organizations.
- **Forum on Lipodystrophy Conference**
  The University of California, San Diego CFAR was involved in organizing a community medical update of information presented at the Lipodystrophy Conference in January 2005. An HIV and clinical trials overview was given to HIV-infected English-speaking women in February 2005 and to HIV-infected Spanish-speaking women in September 2005.
- **HIV and Women: The Female Face of the Epidemic**
  The University of Washington CFAR held a mini-symposium, HIV and Women: The Female Face of the Epidemic, on October 4, 2005. This symposium was attended by more than 100 faculty members, students, and HIV activists. This CFAR developed a course on HIV and women that has expanded over the past year and a half into a new Graduate Certificate Program in HIV and STIs. The comprehensive curriculum addresses the complex interplay of biomedical, social, economic, gender, political, and geographic factors that impact the spread and disease course of HIV and STIs.
- **Keynote Address at the Caribbean Women's Health Association's World AIDS Conference**
  NIAID staff presented the key note address titled The Impact of HIV and AIDS on the African American and Caribbean Women in the U.S. at the Caribbean Women's Health Association's World AIDS Day 2006 Conference in Brooklyn, NY. Findings from the NIAID-sponsored Women's Interagency HIV Study were presented at this conference. More than 100 health professionals attended this event.
- **Women in Science Workshop on International Research Opportunities in Infectious Disease for New Investigators**
  NIAID staff presented a workshop on funding opportunities for international investigators at the Second International Conference on Women and Infectious Diseases, which was held in Atlanta, GA in March 2006. Information on the NIAID-sponsored Comprehensive International

Program of Research on AIDS (CIPRA) was presented to investigators from Africa, Asia and Latin America.

- **Forum on the First National Women and Girls HIV/AIDS Awareness Day**
  Dr. Betsey Harold, an NIAID-sponsored scientist, gave the inaugural address at the first national Women and Girls HIV/AIDS Awareness Day. Her talk was titled Women and Girls HIV/AIDS Awareness Day: A Life Cycle Perspective. The meeting was held at the Lipsett Amphitheater on March 10, 2006. Dr. Harold spoke about the NIAID-sponsored microbicide research program. More than 200 NIH staff participated in this event.

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 that disproportionately affect women including osteoarthritis, osteoporosis, rheumatoid arthritis, temporomandibular joint and muscle disorders (TMJD), fibromyalgia, scleroderma, and systemic lupus erythematosus (lupus). Scleroderma and lupus are diseases in which health disparities have been clearly identified. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

At present, therapies available to treat osteoarthritis are limited. Drug therapies target the symptoms but not the causes of this disease. No treatment inhibits the degenerative structural changes that are responsible for its progression. To further facilitate the development of improved diagnostics and treatments for osteoarthritis, the NIAMS continues to support the Osteoarthritis Initiative (OAI). The first data set from this public-private partnership was recently released and is available to researchers worldwide. Information from the OAI will help to expedite the pace of scientific studies and allow investigators to identify potential new disease targets and develop tools for understanding how to measure clinically meaningful improvements.

Using data from the NIH Women's Health Initiative Observational Study, researchers have found that postmenopausal breast cancer survivors may be at increased risk for bone fractures associated with osteoporosis. Other NIAMS-supported researchers have located a gene that not only influences bone density in mice, but this research also provides new insights into how to preserve bone mass in people. The gene, Alox15, had previously only been linked to fat metabolism and heart disease. This research holds tremendous promise for expanding understanding of the disease and ultimately preventing or slowing disease progression.

Results from a study supported by the NIAMS, the NIH ORWH, and the NIOSH, which is part of the CDC, have broadened the understanding of the effectiveness of surgical versus non-surgical interventions for treating low back pain. Low back pain is one of the most common and frequently debilitating musculoskeletal conditions. In this study, after two years, improvements in levels of reported pain were seen in all patients regardless of their assignment to treatment protocol. However, patients receiving surgery reported having the highest level of improvement across both groups. This information will allow patients and their health care providers to select a treatment intervention based on their preferences.

In recent years, research has led to a new understanding of rheumatoid arthritis and has increased the likelihood that, with time, scientists will find even better ways to treat the disease. Several genetic and molecular components have recently been identified that may prove to be useful therapeutic targets. To better understand the genetic components of this disease, NIAMS-supported researchers examined the genes of identical twins—one with and one without rheumatoid arthritis. Three genes were identified as being over-expressed in patients with rheumatoid arthritis. These findings are exciting because they offer new

insights into the mechanisms by which rheumatoid arthritis is mediated.

One of the greatest tools for researchers trying to understand a disease and test treatments for it is to have a mouse strain that develops problems similar to those of people with the disease. Researchers have used this approach to examine the skin thickening that occurs in patients with scleroderma. Results indicated that a chemical messenger plays a key role in this process. Such information will help scientists design therapeutic strategies for preventing this type of tissue damage associated with scleroderma.

For most people, discomfort from TMJD and muscle disorders will eventually go away with little or no treatment. Some, however, develop significant, long-term problems. Researchers studying a model of TMJD have found that reduced expression of a protein that lubricates the jaw is associated with cartilage damage and could cause joint degeneration. Further investigation revealed that interactions between this protein and certain growth factors could provide additional insight into the development of new, targeted treatments.

Lupus is a complex autoimmune disease, and its cause is unknown. It is likely that a combination of genetic, environmental, and possibly hormonal factors work together to cause the disease. Some lupus treatments lead to early and severe effects of menopause that can contribute to emotional and physical dysfunction. Results of a study supported by the NIAMS indicated that women with lupus may experience the benefits of postmenopausal hormone therapy without an increased risk of severe disease flares. Traditionally, doctors have not prescribed hormone therapy in women with lupus for fear that increasing the level of female hormones in the body might increase disease activity. Additionally, Epstein-Barr virus (EBV) has often been suspected as a trigger for lupus, but recent research has yielded a more direct association. These results provide insights into how the disease begins and have implications for how to treat or even prevent the disease.

Accomplishments

Osteoarthritis

Osteoarthritis, or degenerative joint disease, is the most common form of arthritis. An estimated 12.1 percent (nearly 21 million people) of the population in the U.S. who are age 25 and older have osteoarthritis. Although it is more common in older people, younger people can develop it as well, usually as a result of a joint injury, joint malformation, or genetic defect in joint cartilage. Before age 45, more men than women have osteoarthritis; after age 45, it is more common in women.

Osteoarthritis Initiative Releases Its First Data Set

The Osteoarthritis Initiative (OAI) is a prospective, cohort study on the natural history of this disease. It was established to improve diagnosis and monitoring of osteoarthritis and foster development of new treatments. The first data set has been released. Participants in this study have provided biological specimens (blood, urine, and DNA); images (X rays and magnetic resonance scans); and clinical data (dietary intake, medication use, pain, function, and general health assessments). Making this information available to researchers worldwide will expedite the pace of scientific discoveries and the identification of biological and structural markers (biomarkers) for osteoarthritis. The OAI is a public-private partnership comprised of five contracts funded by the NIAMS, the NIA, the ORWH, the NIDCR, the NIBIB, the NCMHD, and the NCCAM. Private sector funding from Merck Research Laboratories, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Pfizer, Inc., is managed by the Foundation for the NIH

Hyaluronic Acid Shows Potential as a Biomarker for Osteoarthritis

Hyaluronic acid, a lubricating substance within cartilage and the synovial fluid in joints, may be a useful biomarker signaling the presence and severity of osteoarthritis. With support from the NIAMS, the NIA, the CDC, the Association of Schools of Public Health, and the Arthritis Foundation, researchers examined the relationship of blood levels of hyaluronic acid (serum HA) to several factors: x-ray evidence

of osteoarthritis, age, gender, race, body mass index, and various self-reported coexisting conditions (e.g., circulation problems, cancer, gout, high blood pressure, and diabetes). They found a strong association between serum HA and increasing osteoarthritis severity as measured by x-ray of the knees and hips. Regardless of disease severity, serum HA was generally higher in men compared with women and in Caucasians compared with African Americans. These findings emphasize that gender and ethnicity need to be considered in subsequent studies of osteoarthritis biomarkers.

A Spouse Can Help Ease the Pain of Osteoarthritis

NIAMS-supported investigators tested an intervention that combines exercise training with a pain-management program to teach osteoarthritis patients and their spouses strategies for coping with arthritis pain. The intervention can improve not only a patient's level of physical fitness, ability to deal with pain, and self-efficacy (the belief that they can make changes to improve their well-being), but it also increases the spouse's confidence that the patient could cope with arthritis. Once a week for 12 weeks, patients and their spouses were instructed about coping skills and encouraged to practice these skills. The patients also exercised three times a week, and their spouses attended one weekly exercise session to coach their partners in applying pain coping skills during exercise. Other participants in the study were assigned to the pain-management classes, given exercise training three times a week without their spouses, or received their routine care. The investigators found that the patients who attended the pain-management classes—alone or in combination with exercise training—showed improvements in coping and self-efficacy. They found that exercise training—with or without the coping skills classes—improved patients' physical fitness levels and muscle strength. The combination of coping skills training and exercise interventions, however, led to improvements across a much broader range of outcomes than could be achieved through either intervention alone.

Pomegranate Fruit May Have Cartilage-preserving Capabilities

Pomegranate fruit extract can block enzymes that lead to cartilage destruction in osteoarthritis, according to researchers funded by the NIAMS and NCCAM. When the investigators added various concentrations of pomegranate fruit extracts to cartilage samples, they discovered that all but the lowest concentration of the extract inhibited enzymes essential for cartilage cell turnover, degradation, and destruction in osteoarthritis. Although the results suggest that pomegranate fruit extract may inhibit cartilage degradation in osteoarthritis and may be a useful nutritive supplement for maintaining joint health, additional research is needed to identify the active agents in the extract and to determine whether the beneficial effects seen in the lab also occur in the body.

Osteoporosis

Osteoporosis is characterized by low bone mass, bone fragility, and a greater risk for fracture. It is often called a "silent" disease because it lacks discernable symptoms. One out of every two women and one in four men over age 50 will have an osteoporosis-related fracture in their lifetime.

Breast Cancer Survivors Are at Increased Risk for Bone Fracture

Postmenopausal breast cancer survivors may be at an increased risk for bone fractures, according to a recent study supported in part by the NIAMS. Using data from the NIH Women's Health Initiative Observational Study, researchers compared fracture rates of nearly 5,300 breast cancer survivors with those of almost 81,000 women with no cancer history. All participants were postmenopausal and were followed for approximately five years. Data analysis revealed that fracture rates of the spine (only among women who had breast cancer diagnosed before age 55), wrist, and skeletal sites other than the hip were higher among breast cancer survivors. Hip fracture rates, however, were comparable among the two groups of women.

Dental X-rays May Detect Osteoporosis

Scientists are a step closer to developing a new method of screening for osteoporosis, one that may reach a wider number of people sooner than current methods. Researchers investigated several ways to analyze dental x-rays for evidence of osteoporosis. Although the image analysis methods measured jaw bone tissue differently, all methods (Fourier, strut, and wavelet—alone or in various combinations) were useful for distinguishing between women who were known to have osteoporosis and a control group of women who did not have the disease. The combination of Fourier and strut analyses was the most accurate, correctly identifying 92 percent of osteoporosis patients and 96 percent without osteoporosis.

Mouse Genes Provide a Clue to Treating Osteoporosis

NIAMS-supported researchers have located a gene that not only influences bone density in mice but also provides new insight into how to preserve bone mass in people. Because many genes influence bone mass, identifying the specific genes that contribute to osteoporosis has been challenging, especially in humans who are genetically diverse. Researchers studying two strains of mice that have different bone mineral densities discovered that variations in a gene, called Alox15, accounted for a significant part of the differences observed in these animals. The gene had been known for some time, but no one had considered it to be important for the skeleton. Rather, Alox15 was known for its involvement in fat metabolism and was believed to play a role in heart disease. Because humans have two genes that resemble Alox15, scientists believe that one or both might be useful as a target for treatment of osteoporosis. Also, the discovery of the influence of Alox15 on bone mass suggests that a previously unsuspected metabolic pathway could be important for skeletal health. By further studying this pathway, scientists may find additional clues to the prevention of osteoporosis and associated fractures.

Low Back Pain

One of the most common and costly conditions in America is low back pain. It is second only to the common cold in terms of complaints to primary care physicians. An estimated eight out of 10 people will suffer back pain at least once in their lifetime.

Study Shows Patients with Herniated Disks Improve Over Time—Even Without Surgery

NIAMS-supported researchers recently published results from the Spine Patient Outcomes Research Trial (SPORT), the largest trial to date comparing surgical and non-surgical interventions for the treatment of low back and associated leg pain caused by lumbar intervertebral disk herniation. Patients receiving surgery underwent a lumbar diskectomy, a procedure involving the removal, in part or whole, of an intervertebral disk. The non-surgical intervention consisted of physical therapy, education/counseling, home exercise instruction, and nonsteroidal anti-inflammatory drugs. After two years, improvements in levels of reported pain were seen in all patients regardless of their assignment to treatment protocol. However, patients receiving surgery reported having the highest level of improvement across both groups. The results of this study demonstrate that, indeed, lumbar diskectomy is generally effective in relieving pain from herniated disks. But the findings also can reassure patients that, if their pain is tolerable, symptoms will likely subside even without surgery. Patients and their health care providers, therefore, will be able to use the results of this study to help them select a treatment intervention based on their preferences. Additional support for the SPORT was provided by the ORWH and the NOISH.

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 about 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.

Twin Study Reveals Three Genes Involved in Rheumatoid Arthritis

While rheumatoid arthritis is believed to have a strong genetic component, only 15 percent of identical twins both have this disorder. To

better understand differences within twin sets, NIAMS-supported researchers used a sophisticated technique called microarray analysis, which allows scientists to see increases and decreases in the expression of many different genes when comparing people with and without a disease. The researchers examined the expression of more than 20,000 genes at a time in 11 pairs of disease-discordant identical twins (meaning one twin had the disease and the other did not). The most significantly overexpressed gene was laeverin, an enzyme that breaks down certain types of proteins; second was 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), important in a steroid pathway linked to inflammation and bone erosion; and third was cysteine-rich angiogenic inducer 61 (Cyr61), which is known for its role in angiogenesis or the formation of new blood vessels. Identification of these genes yields new, potential therapeutic targets for rheumatoid arthritis.

Newly Identified Molecule Is Implicated in Joint Damage

Rheumatoid arthritis is thought to occur when the body's protective immune system mistakenly attacks the synovium, the thin membrane that lines joints. The resulting inflammation of the joint is a cardinal feature of the disease, but there are other abnormalities, such as overgrowth and attachment of the synovium to bone and cartilage. Unchecked, the synovial tissue can erode the cartilage and bone, leading to joint damage and deformity. Although inflammation has been blamed for this destructive process, a newly discovered adhesion molecule on the surface of the synovial cells, cadherin-11, may also play a role. At normal levels, cadherin-11 enables the synovial cells to stick together and form the lining layer of the synovium. However, when the synovium overgrows, cadherin-11 contributes to cartilage erosion and subsequent destruction of the joint.

Temporomandibular Joint and Muscle Disorders

Temporomandibular joint and muscle disorders (TJMD) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. Some estimates suggest that TMJD affects more than 10 million Americans. The conditions appear to be more common in women than men.

Scientists Identify a Molecule that Lubricates the Jaw

Scientists have demonstrated that a large protein, known as superficial zone protein (SZP), lubricates the jaw. SZP was known to be synthesized and expressed on the surface layer of cartilage in limb joints where it also serves as a lubricant. However, the role of SZP in temporomandibular joint function had been less clear. Researchers studying an animal model of TMJD discovered that reduced expression of SZP is associated with cartilage damage and could cause joint degradation resembling osteoarthritis. On the other hand, when they treated the surface of the cartilage samples with a growth factor called TGF-beta, expression of SZP was enhanced. Because expression of SZP improves joint movement without tissue adhesion, they concluded that TGF-beta could have potential as a therapeutic strategy for TMJD.

Information Dissemination

NIH Osteoporosis and Related Bone Diseases National Resource Center

The mission of the NIH Osteoporosis and Related Bone Diseases National Resource Center (NRC) is to expand awareness and enhance knowledge and understanding of the prevention, early detection, and treatment of bone diseases, as well as strategies for coping with them. The NRC provides patients, health professionals, and the public with important links to resources and information on a variety of bone diseases. Support is provided by the NIAMS with contributions from the NIA, the NICHD, the NIDCR, the NIDDK, the ORWH, and the DHHS Office on Women's Health. Several publications distributed by the NRC have undergone major updates in 2005 and 2006, including:

- Fast Facts about Osteoporosis;
- Fitness and Bone Health for Women: The Skeletal Risk of Overtraining;
- Medications to Prevent and Treat Osteoporosis;
- Osteoporosis: Peak Bone Mass in Women;

- Phytoestrogens and Bone Health;
- Pregnancy, Breastfeeding, and Bone Health;
- What Breast Cancer Survivors Need to Know about Osteoporosis;
- What People with Anorexia Nervosa Need to Know about Osteoporosis; and
- What People with Lupus Need to Know about Osteoporosis.

Other resources under development by the NRC include Check Up on Your Bones, an interactive Web tool designed to provide tailored information about bone health and osteoporosis. Personal "red flags" or comorbities that increase risk for disease (e.g., Crohn's disease, alcoholism, lupus, conditions treated with glucocorticoid medications, and the like) will also be identified. The Web tool will be available in mid-2007. Additional efforts to raise awareness among patients and physicians about conditions that increase the risk of osteoporosis included the distribution of approximately 4,000 promotional cards to physicians, offering a series of fact sheets on these conditions and their links to osteoporosis to use as patient handouts. The NRC has also recently produced a fotonovela (illustrated storybook) titled Isabel's Story: How She and Her Family Learned about Osteoporosis and Bone Health. This publication was designed to educate Hispanic women and their families about the importance of bone health and osteoporosis prevention.

Initiatives

Request for Applications (RFAs)

- **Rheumatic Diseases Core Centers**
  This initiative was designed to provide support to groups of investigators, often from different disciplines, that were taking a multidisciplinary approach to common research problems in rheumatic diseases. The Centers supported through this request for applications fund pilot studies and program enrichment activities and provide core resources and facilities for the investigators to enhance and coordinate their activities. (RFA-AR-05-003, RFA-AR-06-004)
- **Centers of Research Translation**
  The NIAMS developed the Centers of Research Translation (CORT) program to bridge the gap between bench and bedside. The CORTs are designed to bring together teams of basic and clinical researchers in a way that helps translate basic discoveries into new drugs, treatments, and diagnostics. Two of the first four Centers awarded are focusing on areas of research of particular interest to women, including the role of different cell types in the origin and development of lupus and the molecular basis of scleroderma and its underlying causes. (RFA-AR-05-005, RFA-AR-06-003)
- **Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health**
  This solicitation was designed to provide new opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. Each SCOR should develop an interdisciplinary research agenda bridging basic and clinical research on sex/gender factors underlying a priority in women's health. The NIAMS serves as the service center for the administration of this program. (RFA-OD-06-003)
- **Neuroimmune Mechanisms and Chronic Fatigue Syndrome**
  The NIAMS joined several NIH components in this ORWH-led initiative to support research in neuroimmune mechanisms involved in the pathogenesis and pathophysiology of chronic fatigue syndrome (CFS). This opportunity encouraged systems-based approaches for understanding potential interactions of neural and immune systems in the disease process and the impact of alterations in integrated physiological systems on the progression and nature of CFS. (RFA- OD-06-002)

Program Announcements (PAs)

- **Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions**
  This NIDCR-led program announcement was designed to stimulate discovery of etiological and pathophysiological mechanisms underlying chronic, comorbid conditions associated with temporomandibular joint and muscle disorders. (PA-06-188 and PA-06-268)
- **Pathophysiology of Bisphosphonates-Associated Osteonecrosis of the Jaw**
  This NIDCR-led program announcement encouraged studies to determine whether bisphosphonates cause osteonecrosis of the jaw and to elucidate the physiological mechanisms by which osteonecrosis of the jaw manifests in bisphosphonate users. (PA-06-500 and PA-06-501)
- **Mechanisms, Models, Measurement, and Management in Pain Research**
  The purpose of this NINR-led initiative was to encourage research on a wide range of approaches to pain, including pain management, health disparities, molecular and cellular mechanisms, genetics, epidemiology, computer and animal models, and biobehavioral contributions to pain. (PA-06-544)
- **Social and Cultural Dimensions of Health**
  This solicitation, issued by the OBSSR, encouraged research clarifying the role of social and cultural factors in the etiology and consequences of health and illness; linking basic research to practice to improve prevention, treatment, and health services; and exploring ethical issues in health-related social and cultural research. (PA-05-029)
- **Chronic Fatigue Syndrome: Pathophysiology and Treatment**
  This ORWH-led solicitation was created to stimulate research on the epidemiology, diagnosis, pathophysiology, and treatment of CFS. Applicants were encouraged to address age, environmental, and biological risk factors for CFS and the common mediators influencing multiple body systems that are affected by the disease. (PA-05-030)

The NIAMS also participated in the following Broad Agency Announcement (BAA):

- **Innovative Therapies for Rheumatic and Skin Diseases**
  The NIAMS issued this solicitation in December 2005 to accelerate the application of new drugs, biologics, and other interventions in the treatment of rheumatic and skin diseases. This BAA was for support of clinical trials as well as ancillary basic research, and it encouraged research targeting inflammatory or immune mechanisms that cause these diseases. (NIAMS-BAA-05-01)

Health Disparities among Special Populations of Women

Scleroderma

Scleroderma, often referred to as a single disease, is actually a symptom of a group of diseases that involves the abnormal growth of connective tissue supporting the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of the disease. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as heart, lungs, and kidneys. Although scleroderma is more common in women, the disease also occurs in men and children. It affects people of all races and ethnic groups. Because scleroderma can be hard to diagnose and because it overlaps with or resembles other diseases, scientists can only estimate how many cases there actually are in this country. The number of cases of systemic sclerosis estimated in the U.S. ranges from 40,000 to 165,000.

Mouse Model Helps Scientists Understand Fibrosis

Using specially constructed mice with a disease similar to scleroderma, NIAMS-supported researchers have learned more about the skin thickening (fibrosis) that is a characteristic of scleroderma. Researchers created a mouse model of graft-versus-host disease (GVHD), an ailment with similar appearance to scleroderma. Like patients with scleroderma, these GVHD mice developed thickened skin and lung tissue (lung fibrosis). Scientists examined these mice to detect the early signs of the disease and identified a chemical messenger,

transforming growth factor beta (TGF-), that is in higher than normal levels in the GVHD mice and causes their cells to make more collagen (a connective tissue protein), resulting in thicker skin. Such information will help scientists to design therapeutic strategies, perhaps to prevent severe disease and tissue damage.

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 it 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.

Hormone Replacement Not Associated with Severe Lupus Flares

Some lupus treatments lead to early and severe effects of menopause that can contribute to emotional and physical dysfunction. Hormone therapy (HT) is beneficial for both of these side effects. Traditionally, doctors have not prescribed HT for women with lupus for fear that increasing the level of female hormones in the body might increase disease activity. Results of a study supported by the NIAMS indicated that women with lupus may experience the benefits of postmenopausal HT without an increased risk of severe disease flares. Patients taking a standard regimen of HT had no increased risk of severe flares compared to those taking a placebo. Women in the HT group were, however, approximately 20 percent more likely to have a mild-to-moderate flare. Although long-term use of HT is no longer advised for postmenopausal women, the study yields important information for the treatment of early menopause and its most severe symptoms. These results are important in the therapeutic strategy for women with lupus, but further investigation of HT is needed to determine the most appropriate candidates for therapy.

Cancer Drug Holds Promise as a Treatment for Lupus

The cancer medication, rituximab, may someday be a treatment for another devastating disease, namely lupus. In a study of patients with clinically active lupus despite treatment, just one injection of rituximab eased symptoms for up to a year or more. Several participants were able to reduce or completely stop their regular lupus medications. Rituximab, a biological molecule, is FDA-approved for a type of cancer called lymphoma and works by lowering the number of antibody-producing B-cells (part of the immune system) in the body. In lymphoma, the body makes too many B-cells. In lupus, there are usually lower-than-normal levels of B-cells, but they overreact or react inappropriately toward the body's own tissues. All of the participants whose B-cell levels were reduced by rituximab experienced significant reduction in symptoms. Furthermore, the side effects from rituximab were minimal and even reactions to the infusion—a side effect of the drug seen in lymphoma—were not seen in the lupus patients.

Women's Self-management of Lupus

Lupus is a multisystem autoimmune disease of unknown cause that affects women more frequently than men. It also disproportionately affects women of color. Given the wide ranging and varying effects of lupus on individuals, very little is known about living with lupus. A recent study compiled information from women from various ethnic groups (including Hispanic, African American, and Asian American women) who were diagnosed with lupus or had lupus-like symptoms and were being treated with lupus therapies. Results of the study indicated that the core component of living with lupus is managing a medically and socially complex life. The routine activities that encompass the daily events of most women's lives, such as raising children, caring for a family, managing a household, and keeping a job, were complicated by the intrusion of lupus into every aspect of their lives. The context of daily living was surrounded by uncertainty, fatigue, and pain, which interfered with most routine aspects of family life, altered their sense of self, and threatened their financial security. These findings set the stage for further research

and suggest the importance of studying large numbers of African American women, who are most seriously affected by lupus.

Two Proteins Play Surprising Roles in Lupus

Two immune system proteins, Toll-like receptor 7 (TLR7) and Toll-like receptor 9 (TLR9), appear to help the body attack foreign invaders, such as viruses and bacteria, by binding to RNA and DNA, respectively. However, it appears that they can also start reacting to the body's own RNA and DNA, generating autoantibodies, which are the hallmark of lupus and other autoimmune diseases. Mice prone to lupus were bred with mice lacking TLR7 or TLR9. As expected, the lupus-prone mice lacking TLR7 did not make autoantibodies to RNA, and the lupus-prone mice lacking TLR9 did not make autoantibodies to DNA. The lupus-prone mice lacking TLR7 had less severe lupus, but, surprisingly, the lupus-prone mice lacking TLR9 had more severe lupus. This study opens an important avenue to understanding the cause of lupus and identifies TLRs as potential new therapeutic targets.

Researchers Identify Biomarkers for Lupus-related Kidney Disease

Currently, the only way to tell if a patient has renal disease is by taking a biopsy of the kidney. This involves inserting a needle into the kidney and removing a sample of tissue for analysis to determine the exact kind and severity of the disease and the appropriate treatment. Sometimes the biopsy process needs to be repeated. NIAMS-supported researchers analyzed urine samples from patients with lupus, taken just before kidney biopsies, and analyzed them using the technique known as two-dimensional electrophoresis. The process identified several proteins associated with specific forms of end-stage renal disease and indicated the severity of the disease as well as the level of kidney damage. Such noninvasive biomarkers could form the basis of clinical tests that could help doctors to establish an effective treatment plan for these patients without putting them through repeated kidney biopsies.

Common Virus May Trigger Lupus

Epstein-Barr virus (EBV) has often been suspected as a trigger for lupus, but recent research yields a more direct association and may uncover some strategies related to disease prevention. Using serial blood samples, researchers were able to identify when people with lupus began to make the self-destructive autoantibodies that target and damage tissues. In many patients, the antibodies were first produced in response to EBV infection (as evidenced by antibodies to virus). In genetically predisposed people, antibodies revved up to fight the EBV protein cross-reacted with a normal protein fragment in the body called Ro. These autoantibodies mistakenly attacked the patient's own body. The results provide insights into how the disease begins and have implications for how to treat or even prevent the disease, so that the body is retrained and does not attack its own tissues.

Treatment Compliance Barriers in Economically Challenged, Ethnically Diverse Lupus and Rheumatoid Arthritis Patients

Lupus and rheumatoid arthritis are diseases that are complex and difficult to treat. Researchers explored the reason behind worse outcomes among ethnic minorities and economically disadvantaged populations, including increased disability and death. A primary problem in these groups is a lack of compliance with prescribed medical treatments. Through detailed focus groups of economically disadvantaged groups of Hispanic, African American, and non-Hispanic white populations, three consistent themes of non-compliance emerged: fear of side effects, a sense that medications are not effective, and problems navigating the health care system. Additionally, Hispanic patients cited language barriers as being an obstacle in their medical care. Clarification of some of the barriers to effective treatment may lead to strategies to help patients adhere more closely to prescribed treatments, resulting in better medical outcomes.

Lupus Deaths May Be Underestimated in Ethnic Minorities with Low Education Levels

In epidemiologic studies, higher socioeconomic status has been consistently coupled with lower overall mortality and specifically with fewer deaths from cardiovascular and cerebrovascular diseases. Race-specific studies have shown similar associations. Researchers in the intramural research program at the NIAMS wondered whether the incidence of lupus-caused deaths follows the same pattern. Using data on lupus deaths from 1994 to 1997 from the National Center for Health Statistics, the researchers examined the association between education level and incidence of lupus in whites, African Americans, Native Americans, and Asian/Pacific Islanders. Results indicated that, for whites of both genders, the incidence of lupus-caused deaths does decrease as socioeconomic status increases. But in three minority categories—African American men, African American women, and Asian/Pacific Islander women—the risk of death from lupus was lower among those with lower education levels. The researchers also compared the education/mortality link in lupus to that of other causes of death and found that people with lower education levels were underrepresented among deaths from lupus for the three minority categories. The underrepresentation was likely due to underreporting and underdiagnosis.

Ethnicity, Age, and Social Factors Show Significant Correlations with the Level of Disease Activity in Lupus Patients

A recent study revealed that African American and Hispanic patients from Texas had higher levels of disease than Caucasian and Hispanic patients from Puerto Rico. Previous studies showed that genetic and non-genetic factors, such as socioeconomic, psychological, and behavioral variables, were associated with lupus disease activity. To understand the non-genetic factors better, patients with lupus participated in a study which utilized all available medical records, interviews, questionnaires, and physical examinations. High disease activity was more common among African Americans and Hispanics from Texas than among Caucasians and Hispanics from Puerto Rico. Other predictors of high levels of disease activity were increased age, lack of health insurance, helplessness, abnormal illness-related behaviors, and poor social support. The study results indicate that demographic (age, ethnicity), socioeconomic (health insurance), behavioral, and psychological variables are important determinants of high levels of disease activity in lupus. Consideration of these factors may improve the outcomes of lupus treatment.

Information Dissemination

NIH Osteoporosis and Related Bone Diseases National Resource Center Distributes Information for Minority Populations

In addition to the materials described above, the NRC also provided materials developed specifically for minority populations. Publications for African American, Asian American, Pacific Islander, or Latina women included:

- Osteoporosis and African American Women;
- Bone Health and Osteoporosis: A Guide for Asian Women Aged 50 and Older;
- Osteoporosis and Asian American Women; and
- Osteoporosis and Hispanic Women.

Several publications were presented in Spanish, including:

- El Calcio y La Vitamina D: Importantes a Toda Edad (Calcium and Vitamin D: Important at Every Age);
- Haga Ejercicio para Tener Huesos Sanos (Exercise for Your Bone Health); and
- Pruebas de la Densidad ósea: Lo que significan los números (Bone Mass Measurement: What the Numbers Mean).

Lupus: A Patient Care Guide for Nurses and Other Health Professionals

This CD-ROM guide was updated in 2006 and provides an overview of lupus and the elements involved in caring for patients with this complex disease. It is intended primarily for nurses and other health professionals who

work on an ongoing basis with lupus patients. The guide also presents the tools these professionals need to provide the best care possible for this important group of patients with highly individualized presentations of disease, which takes an unpredictable course in each patient.

National Institute of Biomedical Imaging and Bioengineering

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest research institute within the NIH. It was established by law in December 2000. The NIBIB received its first appropriation and grant funding authority in 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 the 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 for 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 FY 2005 and 2006, the NIBIB funded grants 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, such as osteoporosis. 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 FY 2005 and 2006, the NIBIB supported research on women's health in the following disease areas: aging, autoimmune disease, breast cancer, cervical cancer, reproduction, diabetes-related research, obesity, epilepsy, HIV/AIDS, heart disease, osteoporosis, and temporomandibular joint (TMDJ) disease.

Dr. Roderic Pettigrew, the first Director of the NIBIB, began his tenure at the NIH in September 2002. Since his arrival, the NIBIB has reorganized the Institute to facilitate the support of interdisciplinary 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 and subsequently of the Office of Research Administration. Under his purview, Dr. Demsey has responsibility for managing and monitoring all the NIBIB activities that specifically focus on women's health research. In February 2007, Dr. Valery Gordon (formerly of the Office of the NIH Director, Office of Extramural Research) joined the NIBIB and will have responsibility for women's health research oversight. In addition, Drs. Demsey and Gordon direct the efforts of the NIBIB to support research on women's health by serving as the NIBIB representatives to the Coordinating Committee on Research on Women's Health of the ORWH.

Accomplishments

Breast Cancer

Breast Cancer Diagnosis by Electrical Impedance Imaging

This project is in the third 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 (the fraction of negative cases that are properly identified) and sensitivity (the fraction of positive cases that are properly identified) of mammography for breast tumor diagnosis in patients with ambiguous mammograms. Development of algorithms and initial testing of the instrument have begun using phantoms. Testing has also begun to compare the regional impedance spectra obtained with the ACT4 system with biopsy results from patients. Future plans include the addition of cardiac-frequency data to the evaluation. This non-invasive technology poses no known risks to human subjects 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 doctors' efforts to evaluate and treat cancer patients. Research led by Dr. John V. Frangioni of Beth Israel Deaconess Medical Center and Harvard Medical Center is exploring the medical applications of QD that are manufactured to emit light at specific wavelengths in response to illumination. When injected near a tumor in an animal, the QD quickly reveal the sentinel lymph node closest to the tumor. The researchers believe that someday the QD will help illuminate the sentinel lymph nodes in breast cancer patients, thus eliminating the need for multiple biopsies. The QD technique may also improve visualization of cancer cells. Recent research efforts include creating QDs with improved excretion profiles to reduce the toxic side effects of QDs and improving quantitation of biodistribution and pharmacokinetics of QDs.

Parallel Detection and Computation for Diffuse Optical Tomography (DOT) of the Breast

The aim of this work is to develop and assess near infrared diffuse light imaging schemes for tumor detection and characterization. During FY 2003, researchers used a combination of experimental, theoretical, and computational tools and techniques to develop computational schemes for improving the accuracy of three-dimensional (3D) reconstruction and recruiting more high-risk patients for in vivo measurements. DOT reconstruction images of total hemoglobin concentration and scattering have been correlated by radiologists specializing in magnetic resonance imaging (MRI) and categorized into well-correlated, intermediate and poorly correlated cases in terms of tumor position. DOT has successfully distinguished benign from malignant invasive carcinomas in optical contrast studies.

High Spectral/Spatial Resolution Imaging of Breast Cancer

Conventional MRI has good sensitivity but inadequate specificity for detecting breast lesions. The use of high spectral and spatial resolution (HISS) MRI of water and fat signals constitutes a new approach for studying breast cancer. With this approach, the water and fat lineshapes are analyzed to produce images proportional to resonance linewidths, peak heights, areas, and other parameters. HISS will be incorporated into clinical breast imaging protocols to determine whether HISS improves both the sensitivity and specificity of MRI for clinical breast exams.

Reversing Electrostatic Interactions for Improved Gene Delivery

Improved or alternative treatment options are needed for breast cancer. Currently, there is no standard of care for metastatic breast cancer. All first-line combination therapies are regarded as equally efficacious and have a 60 percent response rate. A team of investigators from Boston, Cornell, and Duke Universities is developing a new approach to deliver tumor suppressor genes by reversing electrostatic interaction in amphiphilic systems. With this approach, functional amphiphiles undergo transition from cationic to anionic in cells and release DNA from supramolecular assemblies. The overall goal of these studies is to design, synthesize, and evaluate new charge-reversal amphiphiles to enhance gene transfection efficiency. This system will be tested by attempting to deliver the tumor suppressor gene (p53) to breast cancer cells.

CT Mammography Using Flat Panel Detectors

A Bioengineering Research Partnership between University of Massachusetts Medical School and Lockheed-Martin Corporation

is focused on using tilted charged-coupled devices (CCD) to develop and evaluate a new, high-resolution flat panel mammographic imager with variable pixel size. These studies are supported by the NIBIB and the NCI. The use of this technology has revealed that high-resolution detection in digital mammography is applicable to computed tomography of the breast applications. It appears that the technology under development may have a broader application than the original intent for high-resolution digital mammography.

Speckle-free Transmission Ultrasound for Breast Imaging

The goals of this project are: the development and implementation of a Breast Ultrasound Fluoroscopy System (BUFS), which includes image acquisition and postprocessing for the C-scan ultrasound images; the generation of preliminary tests with a laboratory prototype, the redesign and fabrication of a premarket system suitable for imaging the human breast, and the development of an interface mechanism for the C-scan ultrasound camera and the breast. In early 2004, Imperium scientists and engineers, who serve as system developers for the project, successfully built a higher dynamic range CMOS-base ultrasound sensor. In FY 2005 and 2006, two different C-scan systems were built. The first is a C-scan ultrasound attenuation system designed to examine breast phantoms and breast specimens; there are plans to begin small animal and ultrasound CT studies. The second system is a "dry" BUFS prototype, constructed by Imperium, whose design was modified to enable better coupling of the transducers and capabilities for sensing small image areas that are integrated into a larger breast image using a "stitching" algorithm. The stitching algorithms were developed as a set of Fourier Composition Techniques for integration of C-scanned images. The investigators plan to perform a series of physical tests and imaging performance studies to evaluate the quality of the ultrasound images and to conduct a limited clinical trial (premarket testing) to compare conventional mammography and conventional ultrasound for imaging breast tissue. The investigators expect that a clinically viable system will soon be available for diagnosis of breast cancer.

Breast CT Scanner for Earlier Cancer Detection

Breast cancer is a disease with high incidence in the U.S. and elsewhere, and population-level methods of fighting this disease are aimed primarily at using mammography screening for early detection. While breast computerized tomography (CT) would probably improve cancer detection in all women, some women may have risk factors (e.g., dense breasts, genetic markers, etc.) that require additional screening using breast CT. In this research project, a team comprising medical physicists, physicians, mechanical and electrical engineers, and breast cancer advocates collaborated on the design of the breast CT scanner. The scanner has been built, is operational, and has been evaluated with 65 human volunteers. The next phase of the project will include noise reduction techniques in the preprocessing of the images and will include computer-aided diagnosis tools. Using computer-based observer performance methods, lesion detection performance also will be tested. In addition, a second, more sophisticated breast CT scanner has been designed and constructed, which includes other modalities, such as positron emission tomography (PET) and robotic biopsy guidance. Based on initial imaging, breast CT has enormous potential to detect breast cancer long before metastasis occurs.

Computer-aided Detection for MRI Breast Screening

This project proposes to design, develop, and implement a computer-aided detection system using structural, dynamic, contrast-enhanced, and diffusion-weighted MRI and magnetic resonance spectroscopy for integrating multiple MRI modalities for early detection of breast cancer in high-risk patients. A group of high-risk breast cancer patients willing to participate in clinical trials have been identified at the Huntsman Cancer Institute. Dr. Schabel, the principal investigator, will develop the algorithms and collaborate with clinical radiologists who will provide the knowledge and expertise in interpreting radiologic images against which algorithms will be tested.

Receiver Operating Characteristic (ROC) Analysis for Computer-aided Breast Cancer Diagnosis

The NIBIB funds several projects on ROC analysis for computer-aided diagnosis of breast cancer. ROC analysis is used to evaluate a diagnostic method for sensitivity and specificity. These analytic methods have the potential to improve the accuracy and reliability for breast cancer detection in women. One grant is focused on developing innovative statistical methods for the evaluation and validation of new and low-cost diagnostic modalities. These researchers are evaluating the statistical methods developed in two areas of high importance to women's health: breast cancer predication and assessment of osteoporotic fracture risk. Another NIBIB-funded project is designed to determine whether detection methods optimized in the laboratory can be expected to exhibit the same level of sensitivity in a clinical environment.

Aging and Osteoporosis

Biomaterials for Osteoporosis Therapy

Osteoporosis is a "silent," progressive, and debilitating disease characterized by bone loss, thinning cortical bone, and disorganized trabecular bone that leads to bone fragility and fracture. The goal of the proposed research is to develop novel materials by incorporating magnesium (Mg), zinc (Zn), F (fluoride) ions in a calcium (Ca) phosphate system (Mg/Zn/F-BCP). Separately, these ions have been associated with bone formation, biomineralization, and treatment for osteoporosis. Several methods have been explored to obtain Mg-, Zn-, and F-releasing calcium phosphate matrices. Initially, precipitation and hydrolysis methods were used to obtain more than 70 different preparations. A collaboration between the investigators and Dr. Carmelita Frondoza at Johns Hopkins University used an osteoblast-like cell line for screening Mg/Zn/F-BCP compounds to measure in vitro cell response (principally proliferative capacity). The data indicate that all the preparations tested (approximately 40) show significantly higher proliferative capacity (from 1.5- to four-fold) compared with controls.

A New MR Method to Determine Bone Strength

Osteoporosis is a disorder of the skeleton in which bone becomes abnormally weak and susceptible to fractures. Women may be at greater risk of developing osteoporosis than men in part because they have smaller bone mass or strength. Current diagnosis of osteoporosis using bone density alone does not entirely predict fracture risk because the internal bone structure (i.e., pore size) also contributes significantly to the mechanical strength and, thus, fracture risk. The novel MRI technique developed in this research project will determine the pore size distribution of bone at a micron spatial resolution. Preliminary work demonstrates that the pore-size distribution at this spatial resolution is directly correlated with mechanical properties of the bone. The long-term objective of the research is to incorporate this technique into clinical exams and to validate the method for monitoring treatments for osteoporosis.

Reproductive Health

Temporal-Spatial Biomagnetic Fields of the Fetus

The primary goal of this research is to develop an integrated computer environment for the analysis and display of biomagnetic signals recorded from pregnant women, including anatomical information obtained by three-dimensional ultrasound. Thus far, the major achievement has been the ability to improve the signal-to-noise ratio of the acquired biomagnetic signals using optimal signal analysis technique. A significant outcome is the reliable detection of fetal ST segments, which is potentially valuable because electrocardiogram (ECG) studies in labor have shown that analyses of fetal ST segments are highly correlated with a positive predictive value of fetal distress.

Fetal Functional Magnetic Resonance Imaging

Fetal functional MRI (f-fMRI) has immense potential to further the understanding of normal and pathological fetal neurofunction and development. Studies of the development and application of f-fMRI are motivated in part by the need for monitoring fetuses at risk for intrauterine growth restriction (IUGR). The

purpose of this study is to design, implement, and optimize a technique for blood-oxygen-level-dependent (BOLD) f-fMRI. These techniques involve novel approaches for reducing the field of view of the MRI image and will substantially reduce major artifacts due to fetal and maternal motions. The imaging techniques will be used to compare normal fetuses and fetuses at risk for IUGR.

MRI of Fetal Ventriculomegaly: Morphology and Outcome

Ultrasound (US) is the imaging modality of choice for fetal evaluation. However, there are many cases in which US is non-specific. Further development of US techniques is needed, especially for fetuses with ventriculomegaly (VM). Fetuses with VM are a heterogeneous population, and it is likely that using additional MRI data will facilitate improved counseling and management of these patients. This research is based on the hypothesis that the additional use of MRI with US will improve the diagnostic utility for patients with VM and the ability to predict outcomes, when compared with US data alone.

Initiatives

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-sponsored an RFA to invite applicants to propose 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 by the amount of data that they can collect and their decreased 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 in menopausal women. Recent findings from the Women's Health Initiative do not support hormone therapy for treatment of vasomotor symptoms, and more people are turning to other means to manage hot flashes, including complementary and alternative medicine therapies. (RFA-AT-05-005)

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-sponsored a PA to solicit projects to 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 U.S. Obesity has become an epidemic with gender and health disparity implications and is a major focus of public health efforts at the national, state, and local levels. (PA-05-009)

Conferences and Workshops

- **Prenatal Imaging: Ultrasound and MRI**
  The NICHD, the NIBIB, the Telemedicine and Advanced Technology Research Center, the Gottesfeld-Hohler-Carlson Foundation, and the NIH ORD co-sponsored a workshop to articulate the present research knowledge and gaps in this knowledge for fetal ultrasound (2D, 3D, 4D), fetal MRI, and other fetal imaging technologies. This workshop also sought to define a research agenda for this area. NIBIB-sponsored research was presented by Deborah Levine (fetal MRI of CNS abnormalities and non-CNS abnormalities), Gary Glover (technological improvements in functional fetal imaging), and Curtis Lowery (fetal magnetoencephalography studies of brain development in utero). The meeting was held on September 18-19, 2006 in Washington, DC.
- **Improving Health Care Accessibility Through Point-of-Care Technologies**
  Point-of-care testing has the potential to impact significantly on the way health care is delivered through merging of scientific expertise in miniaturization, imaging, and informatics sciences with knowledge of specific clinical needs in health care settings outside the traditional hospital environment. This area is of particular relevance

to women's health, due to unmet needs in the areas of maternal and infant health and aging-related care. The NIBIB, the NHLBI, and the National Science Foundation (NSF) co-sponsored a workshop, which was held on April 11-12, 2006 in Arlington, VA. This workshop brought together a diverse group of technology developers, clinicians, and clinical researchers to assess the technological developments required for advances in point-of-care testing and to identify high-priority clinical applications that can benefit from a point-of-care approach. Specifically, advances in several technology areas were considered, including sensors and lab-on-a-chip devices, noninvasive patient monitoring, low-cost imaging, health informatics, and telehealth. Clinical needs were addressed in the areas of primary care, emergency medical services, home- and community-based health care, and health care in developing countries. Additionally, representatives from in vitro diagnostics, patient monitoring, imaging, and telehealth industries provided their perspectives on commercializing technologies for point-of-care use. The impact of regulatory and reimbursement issues as well as various topics relevant to the manufacturing of low-cost devices were addressed. Recommendations from workshop participants were used to develop a funding initiative aimed at establishing a network of point-of-care technologies research centers to address the challenges of working at the clinical/technology interface.

Health Disparities among Special Populations of Women

Haptic Interface—Tele-Diagnostics of Breast Pathology

With initial support from the NIBIB to determine feasibility, a finger-shaped tactile sensor was developed and experimentally tested, and a mechanical hand has been developed for breast tumor detection that additionally incorporates an ultrasound probe in the palm. The investigators are now seeking support for the next stages of validation. Ultimately, such a robotic device could be used for breast tumor detection for patients in remote geographical areas who do not have access to physicians.

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. Part of the Institute's mission is dedicated to ensuring that babies are born wanted, timely, and healthy and that they develop to their full physical, emotional, and cognitive potentials. To achieve this mission, the NICHD sponsors research that spans human growth and development, starting from before conception and continuing through infancy, childhood, and adolescence—all critical stages where the foundations for adult health and healthy women are established. Given its mission, the Institute's research aims to overcome many of the complex challenges that face women in addition to those faced by their children and families.

For instance, NICHD-supported research is shedding light on the role that certain genes play in forming fibroids, providing scientists with the preliminary knowledge that they need to begin developing new treatments. In another study, NICHD scientists identified the imbalance of molecules in blood that may be used to predict preeclampsia in pregnant women, a complication that can be fatal. The Institute is also supporting research that has shown a link between the development of endometriosis and the level of environmental chemicals.

The NICHD's advances in women's health are as wide-ranging as the Institute's portfolio, which includes research on infertility, preterm birth, complications of childbirth, HIV infection in women, parenting, and many other scientific areas that are critical to improving the quality of life for women. Highlighted here are just some of the Institute's most recent and significant research activities related to women's health.

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. The Institute's Center for Research for Mothers and Children (CRMC) houses the Obstetric and Pediatric Pharmacology Branch. The Branch coordinates research, clinical trials, and drug development activities for obstetric and pediatric populations to improve the safety and efficacy of pharmaceutical use by pregnant women and children. Also critical 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 Institute also supports research on women and men's reproductive health, with a major focus on women's health. The Reproductive Sciences Branch, housed in the NICHD Center for Population Research (CPR), funds 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 CPR, not only develops new contraceptive methods but also evaluates existing treatments and new therapies, such as microbicides, to determine how they affect women's overall health.

Another branch dedicated to research on 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. This research can save the lives of women and their newborn children.

The NICHD Division of Epidemiology, Statistics, and Prevention Research conducts epidemiologic and other types of research in the areas of fertility, pregnancy complications and adverse pregnancy outcomes, childhood injuries, and birth defects. The division also conducts behavioral research in health promotion; its primary interests include preventing problem behaviors among adolescents, including those that increase risks of motor vehicle crashes.

The NICHD Division of Intramural Research also houses branches conducting women's health research. At the Perinatology Research Branch, researchers are conducting clinical and laboratory research on the role of maternal and fetal inflammation and subclinical infection in preterm births as well as research on prenatal diagnosis of congenital anomalies. The Developmental Endocrinology Branch uses genetic, biochemical, and physiological approaches to shed light on the molecular mechanisms underlying reproductive disorders, such as premature menopause and polycystic ovary syndrome. The NICHD recently appointed Alan DeCherney, M.D. as a Senior Investigator. He will serve as Chief of the new Reproductive Biology and Medicine Branch to lead studies examining implantation, ovarian physiology, and abnormal uterine bleeding. Before joining the NICHD, Dr. DeCherney was a professor at the Department of Obstetrics and Gynecology, UCLA Medical Center. His specialty is in reproductive endocrinology and infertility and gynecology.

Cancer

New Findings Offer a More Complete View of Breast Cancer Gene Mutations in the U.S.

Previous studies of breast cancer focused on families known to be at high risk and on women who develop the cancer at a relatively young age. A large collaborative study now provides the clearest picture yet of the prevalence of mutations in two genes associated with an increased risk of breast cancer. The women involved in the study were a part of the NICHD's Women's Contraceptive and Reproductive Experiences (CARE) study. The sample included white and African American women, ages 35 to 64, who lived in the Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle metropolitan areas. Researchers examined genes called Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2). They estimated that the prevalence of BRCA1 mutations is 0.06 percent, and the prevalence of BRCA2 mutations is 0.4 percent. The most significant predictors for BRCA1 mutations were: Jewish ancestry, a family history of ovarian cancer, and a family history of breast cancer occurring before age 45. For BRCA2 mutations, research-

ers uncovered fewer predictors, and they had more modest effects. Among the breast cancer patients studied, the only significant predictors of a BRCA2 mutation were early age of onset (before age 45) in the patient herself or in her mother, sisters, grandmothers, or aunts.

Reproductive Health

Using Gene Regulation to Treat Uterine Fibroids

NICHD-supported scientists are exploring ways to treat fibroids without surgery. Previously, these researchers identified a multifunctional molecule called transforming growth factor beta (TGF-B) that acts as a major regulator of several processes leading to uterine fibroid growth. Using gene microarray technology—a powerful new tool that allows multiple genes to be examined simultaneously—the researchers identified the different genes that the molecule targets in normal and fibroid cells. Armed with this knowledge, the researchers are testing gene therapy that appears to block production and action of TGF-B. The molecule also has potential implications in other aspects of women's reproductive health, including endometriosis. Ongoing research to discover the function of genes in uterine fibroids may provide further insight into developing novel, non-surgical therapeutic approaches, not only to prevent uterine fibroid growth but also to treat other reproductive conditions. Successful non-surgical therapies for these conditions would eliminate surgical risk and the need for anesthesia, reduce recovery times, and help lower health care costs.

Fibroid Tumors Are Unlikely to Respond to Conventional Hormone Treatments

Fibroid tumors or leiomyomas—the sometimes painful uterine growths affecting many American women—are made up largely of abnormal collagen, a protein that does not respond to reproductive hormones, according to a study by NICHD researchers. The researchers performed a microscopic analysis of fibroid tumors and normal uterine tissue from women who had undergone a hysterectomy for fibroids and found that, unlike normal uterine tissue, the abnormal tissue is not affected by reproductive hormones. The findings suggest that the conventional hormone therapies used to treat fibroid tumors are unlikely to produce much improvement and, at best, will only temporarily relieve symptoms. However, the findings also suggest a strategy for developing a new, non-surgical treatment. NICHD researchers are now planning a study that would test the ability of two drug treatments for uterine fibroids. One drug would block the formation of collagen, in an attempt to keep existing fibroids from growing larger. The second drug acts to break apart collagen fibrils and would be given in an attempt to shrink existing fibroids.

Etiology of Endometriosis

An evolving body of evidence suggests an environmental etiology for endometriosis, particularly involving hormonally active agents such as polychlorinated biphenyls (PCBs). NICHD researchers found that women whose anti-estrogenic PCB levels were high were more at risk for endometriosis compared with women whose levels were low. These outcomes await confirmation in a larger study. A subsequent analysis in the same group of women also found that those with confirmed endometriosis had a lower body mass index, both at the time of diagnosis and historically, than those who did not have the disease. The researchers suggest since the women had a lean body mass over critical windows of adolescence and early adulthood, intrauterine factors may play a role in the etiology of the condition.

Popular Contraceptive's Effect on Bone Loss Is Reversible

The potential impact of taking hormones is one of the many factors that influence a woman's choice of contraceptive method. To provide women and clinicians with more reliable information on which to base these decisions, the NICHD has supported several studies to evaluate the impact of Depo-Provera (depot medroxyprogesterone acetate or DMPA) on bone density in women of various ages and racial groups. DMPA is an injectable hormonal contraceptive that lasts for three months. Researchers compared the bone densities of healthy adolescent females who were already using DMPA to the bone densities of a group that was not using the product. The study focused on younger women because approximately 10 percent of adolescents

(compared to 3 percent of women overall) use DMPA as a contraceptive and because women develop most of their bone mass during their adolescent years. The researchers found that, although bone loss occurs while using DMPA, the young women fully regained their bone density after discontinuing use of the product. DPMA is more than 99 percent effective and is the only injectable contraceptive available in the U.S. This research should help women choose reliable, practical contraceptives with the assurance that they need not increase their future risk of osteoporosis or bone fractures.

Pelvic Floor Disorders Research Network

Combined Surgery Reduces Incontinence in Women with Pelvic Organ Prolapse

By performing two surgical procedures during the same operation, researchers at NICHD's Pelvic Floor Disorders Research Network reduced by half the incidence of urinary incontinence in women with a condition known as pelvic organ prolapse. The condition occurs when the pelvic muscles and connective tissue within the pelvic cavity weaken or are injured, and the uterus, bladder, and bowel press down on the vagina, causing it to invert. To treat pelvic organ prolapse, gynecologists may recommend that patients have a surgical procedure known as sacrocolpopexy, where surgical mesh and sutures are used to anchor the vagina to the sacrum. However, after sacrocolpopexy, many women experience incontinence, which makes them candidates for a second surgical procedure, the Burch colposuspension, where additional sutures are sewn through the wall of the vagina and anchored to ligaments inside the pelvic cavity, near the pubic bone. The Network investigators showed that proactively performing the Burch colposuspension at the same time as sacrocolpopexy proved effective at preventing incontinence in women with prolapse who did not have symptoms of stress incontinence before surgery, allowing women to both maintain their quality of life and avoid a second surgery.

Pregnancy

Molecules in Blood Foretell Development of Preeclampsia

Preeclampsia is a life-threatening complication of pregnancy that often occurs without warning. The only treatment is delivery of the baby, which can result in a preterm birth and its associated complications for the infant. New research findings present strong evidence that an imbalance of two proteins produced by the placenta is responsible for the symptoms of preeclampsia (e.g., high blood pressure and protein in the urine). Abnormally high levels of these proteins appear to deprive the blood vessels of substances needed to keep the lining of the blood vessels healthy. Deprived of these essential substances, the cells lining the blood vessels begin to sicken and die. As a result, the blood pressure increases, and the blood vessels leach protein into the tissues and urine. Detecting high levels of these proteins early in pregnancy may help to predict the later development of preeclampsia and may also help to distinguish preeclampsia from chronic high blood pressure, kidney disease, and other conditions that can produce symptoms similar to preeclampsia.

Risk with Vaginal Delivery after a Cesarean Birth Is Low

The risks from vaginal delivery after a prior Cesarean delivery are low but are slightly higher than for a repeat Cesarean delivery. This finding is from the largest, most comprehensive study of its kind ever conducted. In 2002, one of every four American infants was delivered by Cesarean section, a marked difference from 1970, when only one of every 20 infants was a Cesarean birth. This increase in Cesarean deliveries, however, highlights an important medical question faced by millions of women each year: Once a woman has delivered by Cesarean, what procedure is best for her for future births? Anecdotal accounts of uterine rupture and other problems frightened expectant mothers away from attempting vaginal births for subsequent pregnancies, but were they making the best decision? To answer this question, NICHD scientists studied the records of more than 30,000 women and found that the risk of adverse outcomes from a vaginal delivery after a prior Cesarean delivery is low.

This large-scale study provides important information for women and their physicians when deciding whether to have a vaginal or repeat Cesarean delivery.

Labor Takes Longer for Overweight and Obese Women

Pregnant women who are overweight or obese progress through labor more slowly than do normal weight women. Since a longer labor is one consideration for whether or not a pregnant woman will have a Caesarean section, the new finding also means that a physician may need to take a woman's weight into account before deciding whether or not to recommend the procedure. When taken together with other findings showing that extra body weight during pregnancy can pose serious and even life-threatening complications for both mother and infant, the current finding underscores the need for overweight or obese women who are either pregnant or contemplating pregnancy to seek medical attention.

Improving Drugs for Pregnant Women

The NICHD Obstetric-Fetal Pharmacology Research Network was established with support from the ORWH to provide the expert infrastructure needed to test therapeutic drugs during pregnancy. The Network is completing one of its first translational studies. The research examines the safety and efficacy of glyburide, which is used to control the blood sugar of pregnant women who have developed gestational diabetes. Gestational diabetes can lead to stillbirth or to poor birth outcomes for infants and to infections, high blood pressure, and preeclampsia in mothers. The Network is also set to launch a new clinical trial of a progesterone treatment, a promising therapy for high-risk pregnant women. Past studies showed that weekly injections of the drug could reduce the risk of preterm birth by approximately one-third in women with a history of preterm birth; however, more data are needed on appropriate dosage, how the drug is metabolized during pregnancy, and the drug's impact on the ability to monitor pregnancy by using different biomarkers.

New Treatment That Can Prevent Postpartum Hemorrhage in Community Settings

In developing countries where women deliver outside of hospital settings, a drug called misoprostol has the potential to prevent maternal death due to postpartum hemorrhage from complications of pregnancy and childbirth. While injecting oxytocin is the standard of care to prevent postpartum hemorrhage in many hospitals, the treatment may not be available in homes or basic medical facilities. The NICHD supported a research team that conducted a randomized trial in rural India and found that misoprostol reduced blood loss. The cost of the drug may reach $1 per dose, making misoprostol a cost effective way to save lives. The government of India is scaling up use of misoprostol to prevent postpartum hemorrhage.

Miscarriage

A Drug Offers Women an Alternative to Surgical Treatment after Miscarriage

Misoprostol, a drug first used to reduce the risk of stomach ulcers in people taking certain types of painkillers, now also offers an alternative to surgery after miscarriage. Previously, doctors relied on a procedure called vacuum aspiration to prevent complications and clear the uterus following miscarriage. In seeking a less invasive treatment, some doctors began using misoprostol, which can cause uterine contractions. No large-scale trials, however, had evaluated the safety and effectiveness of the drug as a followup to miscarriage until NICHD researchers collaborated in a study with four U.S. university hospitals. The study demonstrated that misoprostol was nearly as effective as vacuum aspiration and was well-accepted by the women who used it. The drug is appropriate for use on an outpatient basis as an effective, safe, acceptable, and economical alternative to surgery after a miscarriage. Misoprostol also offers hope for improving the health of women in developing countries where financial resources and access to medical facilities are limited, making medical treatment after a miscarriage difficult to obtain.

Preventing Miscarriage

Infertility affects millions of women in the U.S. One potential cause of infertility and a primary cause of miscarriage is an error in meiosis, the complex process that halves the number of chromosomes in eggs and sperm to prepare for conception. Errors in meiosis can lead to the death of the affected egg or miscarriage of a resulting embryo that contains an incorrect number of chromosomes. Recently, a team of researchers confirmed the identity of a receptor on the egg, Gpr3, which ensures that the egg waits for the proper signal before it divides its chromosomes in preparation for meeting a sperm. If the egg is missing Gpr3 or unable to activate the Gpr3 receptor, it cannot receive the signal and starts splitting early. With this knowledge, there is now a firm base to discover how other signals that are linked to the process may be regulated by hormones throughout the menstrual cycle. Identifying Gpr3 adds another piece to the puzzle surrounding human reproduction and suggests new ways for treating female infertility and preventing miscarriages.

Women and Families

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 experienced physical or sexual abuse in childhood or as adults are less likely to be married or in stable relationships, compared with women without a history of abuse. Although unemployment and shifts in society's view of marriage and cohabitation are often said to contribute to low marriage rates, the study findings show that the consequences of abuse are also significant factors. Women who were abused as adults tended to avoid romantic relationships with men and to focus their energies on raising their children and on learning and personal development. These women often had the resources needed to avoid abusive men, such as steady employment and a support network of family and friends. Women who were abused as children tended to have a series of short-term relationships and were not consciously aware of the connection to the abuse they experienced with men. The researchers suggested that the degree to which abuse interferes with family formation in the U.S. may be substantially underestimated, and policies to foster stable homes should attempt directly to reduce the prevalence of abuse.

HIV/AIDS

Breastfeeding and Maternal Mortality

Several years ago, a small-scale clinical trial in Kenya raised concerns that the simple act of breastfeeding her baby could increase an HIV-infected woman's risk of dying within two years of giving birth. Since this finding proved counter to those from other studies, NICHD-supported scientists analyzed data from clinical trials involving more than 4,000 HIV-infected women to resolve the concern. The researchers found no evidence of an increased risk of death in HIV-infected mothers who breastfed their infants. In addition to laying to rest concerns about premature death, the study found that women who breastfed for longer time periods actually had a lower risk of dying. These results and other important factors should reassure HIV-infected women that they can safely breastfeed their infants without increasing risk to their own health.

Tissue Engineering

Tissue-engineered Follicles Produce Live, Fertile Offspring

Oocytes, or nearly mature eggs, grown outside of the female body are of poor quality and yield few births, which limits a woman's ability to store eggs to preserve her fertility. To address this issue, NICHD-supported researchers applied tissue-engineering principles to sustain and mimic the follicular environment in the body in a culture of immature mouse follicles maintained in a laboratory. The scientists were able to develop mature oocytes similar to oocytes matured within the body. Furthermore, when these embryos were fertilized in vitro and transferred to female mice, they produced both male and female offspring, which were also fertile. This innovative system creates new opportunities for discovery in follicle biology and establishes a core technology for human egg banks to preserve fertility.

Training

Annual Summer Institute in Maternal-Fetal Pharmacology (Summer Institute)

Pregnant women and their unborn babies are rarely included in therapeutic studies, excluding them from the benefits of appropriate drug therapy. To fill this gap, the NICHD began a new week-long course targeted at clinical and non-clinical scientists considering academic careers in studying therapeutics during pregnancy, the perinatal period, and lactation. Partners include the NIH ORWH and the Institute of Human Development, Child and Youth Health at the Canadian Institutes of Health Research. Each participant develops a preclinical or clinical drug therapy protocol before the course and then discusses it among peers and faculty members during the course. By combining interactive, hands-on learning with expert lectures, the Summer Institute will foster the development of a critical mass of researchers and clinicians in the neglected area of maternal-fetal pharmacology.

Clinical Research/Reproductive Scientist Training (CREST)

In collaboration with the Clinical Research Training Program at Duke University and the American Society for Reproductive Medicine, the NICHD offers a training program to meet the need for formal academic training in the quantitative and methodological principles of clinical research in reproductive medicine. Designed specifically for physicians in private or academic clinical practice in reproductive medicine, this innovative program engages the practicing physician in clinical research while allowing the individual to maintain an active role in clinical practice.

Initiatives

Request for Proposals (RFPs)

- **Consortium on Safe Labor**
  In the past 50 years, labor and delivery practices have been influenced by the Friedman Curve, a mathematical model of how the stages of labor should progress during normal delivery that was originally created in the early 1950s. However, labor management has changed substantially since then, in part, reflecting changes in the obstetric population, such as increased obesity and more advanced age. To determine the usefulness of the Friedman Curve to modern obstetrics, NICHD researchers reevaluated the labor curve and found that the definitions of labor protraction and arrest were too stringent for contemporary clinical management of childbirth, therefore underscoring the need for new evidence-based definitions of labor protraction and arrest. To address this gap, NICHD researchers are planning a large multicenter observational study to collect existing medical record data on approximately 200,000 deliveries from several U.S. hospitals. The study will involve digitized tracings of labor progress from patients at multiple hospitals. The researchers will then collate and merge the data electronically with postpregnancy and neonatal records. Advanced statistical methods will allow the researchers to examine labor progression and to possibly redefine labor protraction and arrest. The ultimate goal is to identify a meaningful point at which surgical intervention is needed, which may have a profound effect on decisions about the need for Cesarean delivery.
- **ENDO Study (Endometriosis: Natural History and Diagnosis)**
  Building on evidence that supports an etiologic link between environmental chemicals and endometriosis, NICHD researchers launched a study to assess whether exposure to polyhalogenated aromatic hydrocarbon chemicals, a class of persistent environmental chemicals capable of accumulating in the food chain, is linked with the incidence and severity of endometriosis in women. The study will include women who have endometriosis and undergo laparoscopy (a procedure that allows a health care provider to look directly at the organs in a patient's abdomen or pelvis), and control groups. Visceral fat samples will also be collected to measure the amount of chemical exposure. The findings will help researchers to better understand what environmental factors contribute to the development of endometriosis and enable them to propose strategies for treatment.

- **The Effects of Aspirin in Gestation and Reproduction (EAGR) Trial**
  NICHD researchers launched a trial involving women with a history of miscarriage to evaluate the efficacy of aspirin treatment to prevent pregnancy loss. Aspirin has effects on inflammation and blood flow and has been used in certain groups of women to improve reproductive outcomes. For example, aspirin treatment for infertility has been shown to improve the condition of the lining of the uterus. In vitro fertilization (IVF) studies seem to suggest that aspirin supplementation improves the rate of implantation and pregnancies. However, there is conflicting results among women with recurrent miscarriage. To help clarify the issue, NICHD researchers will evaluate the effect of aspirin throughout implantation, fetal development, and delivery among women with one recent miscarriage. The findings could promote a simple treatment that may help to overcome barriers to implantation and reduce the risk of miscarriage.
- **Bone Mineral Density in Childhood Study--Peak Bone Mass**
  The NICHD is extending its bone mineral density study to determine at what stage of development bone mass reaches its peak. Early study findings show that bone minerals continue to accrue beyond the teenage years so the study will continue to follow the adolescents participating in the study to young adulthood. The bone mass data will be useful in furthering research on identifying children and young adults who are at risk for osteoporosis, which is a major health concern for women.

Request for Applications (RFAs)

- **Pelvic Floor Disorders Network**
  The NICHD is leading a national program, in collaboration with the NIDDK and the ORWH, designed to investigate problems in women with pelvic floor disorders, including pelvic organ prolapse, urinary incontinence, fecal incontinence, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tracts. In many cases, clinicians have adopted principles of care and surgical techniques before rigorous, objective, controlled evaluation has been conducted. The Network is evaluating outcomes of different management strategies: surgical versus non-surgical, timing of interventions, and postoperative management. (RFA-HD-05-019)
- **Cooperative Multicenter Reproductive Medicine Network**
  The NICHD and the ORWH support an ongoing cooperative program designed to conduct clinical studies investigating problems in reproductive medicine, including infertility, gynecological disorders and diseases, diseases and disorders of the male reproductive system affecting fertility, and endocrinological disorders affecting reproduction. (RFA-HD-06-008)
- **Contraceptive Development Research Centers Program**
  The aim of this program is to conduct a wide range of research, both basic and applied, with the ultimate goal of developing clinically useful contraceptive products. (RFA-HD-06-014)
- **Cooperative Reproductive Science Research Centers at Minority Institutions**
  The NICHD and the ORWH are supporting a program to 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 high-priority topics in reproductive health, including women's health. (RFA-06-HD-017)
- **Global Network for Women's and Children's Health Research**
  To address the urgent health needs and public health problems of women and children in resource-poor countries, the NICHD partnered with the Bill and Melinda Gates Foundation and multiple NIH ICs to establish an international research network to improve the health of women and children. Network researchers design, implement, and evaluate evidence-based health interventions to reduce morbidity and mortality associated with pregnancy and early childhood. The goal is to create sustainable research infrastructures and public health capabilities in developing

countries. To do this, network researchers are encouraged to collaboratively design, develop, and conduct multiple simultaneous common clinical trials as well as to implement and evaluate evidence-based health interventions and pertinent formative and translational research studies. (RFA-HD-05-025)

Program Announcements (PAs)

- **Vulvodynia - Systematic Epidemiologic, Etiologic or Therapeutic Studies**
  The NICHD and the ORWH are encouraging basic, clinical, translational, epidemiological and/or behavioral research relevant to vulvodynia that advances prevention and therapeutic opportunities. (PA-06-302)
- **Indo-US Program on Maternal and Child Health and Human Development Research**
  The Republic of India and the U.S. share a strong commitment to improve the health and well-being of women, children, and adolescents by expanding cooperative biomedical and behavioral research through a cooperative program of maternal and child health and human development research. Collaborative research projects will be designed to achieve enhanced maternal and child health, disease prevention, product development, and/or technology transfer. The program places specific emphasis on the need for more "translational" types of research intended to move beyond basic science and discovery to product development and delivery. (PAR-06-196)
- **Indo-US Program on Contraception and Reproductive Health Research**
  The goal of this program is to support collaborative research that will result in expanded contraceptive options and improved reproductive health in the U.S., India, and globally. Like the Maternal and Child Health and Human Development Research initiative, specific emphasis is placed on the need for more "translational" types of research intended to move beyond basic science and discovery to product development and delivery. Projects will be designed to achieve enhanced reproductive health, disease prevention, product development, and/or technology transfer. (PAR-06-197)
- **NICHD Institutional Predoctoral Training Program in Reproductive, Perinatal, and Pediatric Epidemiology**
  In response to the Society for Pediatric and Perinatal Epidemiology, the NICHD established a new training program designed to fill the need for well-trained epidemiologists in reproductive, pediatric, and perinatal medicine. Using T32 institutional training grants, the program supports three years of broad and fundamental research training for predoctoral candidates. Program participants are exposed to both the foundational training necessary to become proficient epidemiologists and opportunities to acquire clinical knowledge of reproductive, perinatal, and pediatric health issues. As the first cohort of trainees progress to graduation and new cohorts fill slots each year, the NICHD training program will begin fulfilling its objective of producing a well-qualified cadre of academic and research investigators capable of research excellence. (PAR-05-130)

Conferences and Workshops

- **Advances in Leiomyoma Research: 2nd NIH International Congress**
  The NICHD, in collaboration with the ORWH and other NIH IC and Federal agencies, sponsored a conference in February 2005 to bring together researchers working in the field of biomedicine, epidemiology, basic and clinical research, therapeutics, and translational medicine to exchange scientific information among members of the uterine leiomyoma research and health care communities.
- **2005 Research Meeting of the Specialized Cooperative Centers Program in Reproduction Research**
  The NICHD holds a biennial meeting of the Specialized Cooperative Centers Program in Reproduction Research (SCCPRR). This NICHD program is a national network of centers designed to foster multidisciplinary collaborations among basic and clinical scientists conducting research on reproduction, with the goal to improve human reproductive health by speeding the transfer of basic science findings into clinical practice. The April 2005 meeting featured

research presentations by SCCPRR investigators, trainees, and their collaborators as well as by investigators supported by the National Cooperative Program for Infertility Research.

- **Infertility Treatment and Adverse Pregnancy Outcomes**
  Recent evidence shows higher rates of adverse pregnancy outcomes in singleton and multiple pregnancies associated with assistive reproductive technology, such as low birth weight, preterm delivery, fetal growth restriction, and genetic disorders. In September 2005, the NICHD held a workshop to discuss the roles that the underlying infertility and the effects of the infertility treatments may play in pregnancy outcomes.
- **NIH State-of-the-Science Conference: Cesarean Delivery on Maternal Request**
  In 2004, the rate of Cesarean delivery in the U.S. reached 29.1 percent, the highest ever, and limited evidence suggested that increasing numbers of such deliveries were performed on maternal request. In March 2006, the NICHD and the NIH OMAR sponsored a conference to examine evidence on how frequently Cesarean deliveries are scheduled for women without medical or obstetrical indications for the procedure, and how these "maternal request" deliveries compare with vaginal delivery in terms of child health and development and maternal health outcomes. (See http://consensus.nih.gov/2006/2006CesareanSOS027main.htm.)
- **Women's Reproductive Health Research (WRHR) Career Development Program: Scholars' Research Symposium**
  The program held its annual scholars' meeting in June 2006 at the Wayne State University School of Medicine, which is also home to the NICHD's Pregnancy Research Branch. The program provides the opportunity for obstetrician/gynecologists who have recently completed their postgraduate clinical training to further their education and experience in basic, translational, and clinical research.

Health Disparities among Special Populations of Women

Reducing Disparities in Infant Mortality

The NICHD continues to work with communities on the development of outreach materials and programs to reduce the risks of sudden infant death syndrome (SIDS). While the rate of SIDS among all groups has declined by more than 50 percent since the Back to Sleep Campaign began, African American, American Indian, and Alaskan Native infants are still more than twice as likely to die of SIDS as white infants. To address this disparity, the NICHD engages in special outreach initiatives and develops public education materials to reach the high-risk communities.

Outreach to American Indian and Alaska Native Communities

The NICHD collaborated with American Indian and Alaska Native communities to begin development of culturally sensitive educational materials to reduce the risk of SIDS. Working together with the Indian Health Service and tribal stakeholders, the Institute is developing an outreach toolkit that will enable individual tribes and communities to personalize and convey SIDS risk reduction messages in their native languages.

Outreach to African American Communities

Partnering with stakeholders across Mississippi, the Institute supported training for county, district, and state health department employees on SIDS risk reduction guidelines, particularly those most recently updated by the American Academy of Pediatrics (AAP). The Institute also collaborated with the SIDS Coalition of Ohio to sponsor a SIDS Risk Reduction Sunday, using church leaders to raise awareness of SIDS among congregations across the state. In addition, the NICHD partnered with First Candle/SIDS Alliance and the NINR to launch a continuing nursing education curriculum to teach nurses about SIDS risk reduction behaviors, ways to convey these guidelines to their patients, and recent research findings and AAP recommendations.

In January 2006, as part of the NIH Public Trust Initiative, the NICHD and the NINR led an NIH team to listen, learn, and talk about

health in Mississippi with the overall goal of reducing health disparities. The NIH team partnered with the Alpha Kappa Alpha Sorority to organize the weekend event and to honor the sorority's long-term commitment to providing health services and to taking health messages to their diverse membership and the people of Mississippi.

Conferences

Health Disparities in Infertility

In March 2005, the NICHD, the OBSSR, and the ORWH supported a conference to convene demographers, clinicians, and related researchers to examine the prevalence and receipt of infertility services by minority and low-income populations. The overall goal of the conference was to encourage future interdisciplinary collaborations. In the U.S., the costs of infertility treatments are borne primarily by the couples, and those who seek treatment are generally white, older, married, and with middle-to-high incomes. Emerging evidence suggests that variation in treatment response to artificial reproductive technology and causes of infertility may vary by racial/ethnic group.

Addressing Health, Educational, and Socioeconomic Disparities of Children in Immigrant Families

More than one in five children in the U.S. today grows up in an immigrant family, either immigrants themselves or the children of immigrants. Examining health disparities in immigrant families is essential to understanding disparities in health, education, and other types of well-being among populations across the nation. The May 2005 workshop brought together researchers conducting studies on immigration and immigrants to discuss major accomplishments in the field so far; to identify the gaps in knowledge, methodology, and data that still exist; to promote interdisciplinary communication, cooperation, and collaboration; and to build a research agenda. The meeting was supported by the NICHD, the NIH OBSSR, and the Bureau of Citizenship and Immigration Services of the Department of Homeland Security.

Trans-NICHD Maternal Obesity and Reproductive Health Workshop

The Institute also addresses important public health issues that transcend an individual center's activities and require multiple, varied, and often creative approaches to problem solving. The NICHD convened a workshop in June 2006 to address the understudied yet growing impact of maternal obesity on reproductive health, pregnancy and birth outcomes, and subsequent maternal and infant health. Special emphasis was placed on racial and ethnic minority groups that are at increased risk for obesity and its adverse health outcomes. This innovative NICHD effort not only included the usual goals of a scientific meeting—reviewing the state of the science, identifying knowledge gaps, and developing a research agenda—but also added a public health perspective to develop a process that can begin translating research findings into public health initiatives. Workshop participants were asked to identify several evidence-based messages that could be developed into meaningful public health campaigns and to identify barriers that could be overcome to facilitate the adoption of the messages in minority communities. To this end, a diverse group of scientific research experts, practitioners, and advocates from minority communities were brought together to contribute their unique insights to inform the discussion. Based on the messages identified at the meeting, the Institute plans to work not only with researchers to address important scientific questions but also with community leaders and stakeholders to develop meaningful and culturally relevant public health campaigns, which will then be implemented by leaders and practitioners in their own communities. The format of this successful workshop could serve as a model for similar scientific meetings that the Institute sponsors in the future.

Gender Analysis

Gender-Specific Treatment of Pediatric Cardiac Arrest

Cardiac arrest can lead to a lack of oxygen delivery to the brain and result in brain damage or death in children. Preliminary data from brain cells in culture show gender

differences in metabolism and the process of cell death in the injured brains of a rat animal model, which may have implications for treatment in girls and boys. To address the issue, NICHD began funding a study that will use animal models and brain cell cultures to examine whether the pathways to brain damage are gender specific. The findings will allow future researchers to determine whether novel therapies that target specific molecules would differ in mediating or preventing brain damage in girls and boys.

Concurrent Partnership Patterns in the U.S.

The Institute also began funding a study for a multilevel examination of concurrent partnerships (having more than one partner during a given period of time) among men and women. The researchers will examine gender differences in several aspects of concurrent partnerships: (1) the patterns; (2) how individual, relationship, and community characteristics influence the risk of beginning and ending the partnerships; and (3) how partner characteristics and HIV-risk behaviors, including alcohol and drug use, affect the formation of the partnerships. The findings will shed light on changes in the patterns of concurrent partnerships and in HIV-risk behaviors over time, which could be used to develop novel HIV-risk prevention or reduction interventions.

The Effect of Male and Female Passengers on Teen Driving

Vehicle crash rates for teenage drivers are higher in the presence of teen passengers. To better understand the reasons for these higher crash rates, NICHD researchers conducted a study to learn how the presence of teen passengers might affect teen driving behavior. The researchers found that teenage drivers—both males and females—were more likely to tailgate and exceed the speed limit if there was a teenage male passenger in the front seat. Conversely, male teenagers were less likely to tailgate or exceed the speed limit when a teenage female was in the front passenger seat. In addition, female teen drivers were slightly more likely to tailgate if there was a female teen passenger in the vehicle with them. The study could not identify why teens were more likely to engage in more risky driving behavior in the presence of teen passengers. To find answers, NICHD researchers are designing a study that will involve placing electronic monitoring equipment in vehicles with teen drivers. After learning the reasons for the risky behavior, researchers can then work to develop ways to prevent it.

Study Confirms Finding That Males and Females Use Different Parts of the Brain for Performing Language and Visuospatial Tasks

NICHD-supported scientists confirmed, by using functional magnetic resonance imaging, that men and women use different areas of the brain when processing both language and visuospatial information. During the tests, the men and women performed equally on tasks; they just used different parts of their brains to get the tasks done. This study can pave the way toward understanding the extent to which sex differences are developmental, sociological, and/or hormonal and which differences may become more or possibly less distinct with age. Furthermore, knowledge of gender differences in normally functioning brains is essential for understanding what may go wrong during development.

Meeting on Love, Marriage, and HIV: Gender and HIV Risk

The NICHD held a meeting in December 2005 where investigators presented research conducted in five countries. Presentations examined how women's and men's marital status and marital expectations vary across cultures and how that interacts with HIV risk.

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 and infectious 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 diseases, and recurrent herpes lesions; oral manifestations of osteoporosis and other bone diseases; salivary gland dysfunction and disease; craniofacial birth defects and developmental disorders; and connective tissue diseases and disorders.

The NIDCR has a long tradition of support and leadership in the field of pain research. The Institute's work in pain research includes conditions where gender-based differences have been reported, such temporomandibular joint and muscle disorders (TMJDs). Researchers have found that the prevalence of back pain, headache, and pain associated with TMJDs increases significantly with increasing pubertal development in girls, but only back pain increased significantly in boys. Thus, for girls, pubertal development was a better predictor of pain than age. During FY 2006, the NIDCR funded the first, large, prospective clinical study to identify risk factors that contribute to the development of TMJD. That study, the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), will open a critical and largely unexplored window on the early stages of the disorder, pointing researchers toward possible targets for better treatments to control pain.

The NIDCR's commitment to the fundamental study of the body's hard tissues, such as 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. Among the NIDCR's efforts in this area are studies that are characterizing the TMJ disk at tissue and cellular levels, thus providing vital information that will one day allow for biological approaches to reconstruct or regenerate the temporomandibular joint.

Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the Institute has long emphasized the importance of genetic, behavioral, social science, and epidemiological research. Genetic studies on the area of pain include the haplotype mapping of catechol-O-methyltransferase (COMT) and responses to specific pain-evoking stimuli. Three common haplotypes in the COMT gene have been identified, and they relate to the threshold and tolerance to thermal, ischemic, and mechanical stimuli and temporal summation to heat pain.

The association between periodontal diseases and systemic effects continues to be a high priority for the NIDCR. For example, the NIDCR is supporting clinical trials on maternal periodontal infections and whether or not they represent a bona fide risk factor for preterm birth and growth restriction. Other evidence suggests that periodontal disease and its progression may represent an infectious and inflammatory exposure that could have serious deleterious effects during pregnancy. The NIDCR sponsored two large, randomized trials designed to determine if non-surgical treatment of periodontal disease during pregnancy reduced the incidence of preterm birth and associated growth restriction. Both the Obstetrics and Periodontal Therapy (OPT) trial and the Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) trial were designed to determine whether pregnant women having non-surgical periodontal therapy during the second trimester of pregnancy had fewer premature and/or low-birth weight infants when compared with women having periodontal therapy after delivery. Results from the OPT trial were published recently in the New England Journal of Medicine and indicate that pregnant women who received non-surgical treatment for their periodontal disease did not lower significantly their risk of delivering a premature or low birth-weight baby. Non-surgical or standard periodontal treatment involves thoroughly cleaning of the teeth above and below the gums, commonly called scaling and root planning. This study also evaluated the safety of general dental care during pregnancy. It found that dental treatment through the second trimester—both general and periodontal care—did not increase the number of adverse events for women during pregnancy. However, for the first time, the safety of providing periodontal care to women in their second trimester was established.

Overall, research advances that affect women in particular are to be found within many of the Institute's broad research categories. This report highlights the accomplishments and initiatives in the areas of chronic pain, temporomandibular disorders, osteoporosis and basic bone biology, autoimmune

disease, HIV infection, health disparities, craniofacial anomalies and periodontal diseases, and systemic effects.

Accomplishments

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 may be due to hormonal influences. Animal and human studies include research on the following areas.

Kappa Opioid Receptors

Differences exist in the distribution of kappa opioid receptors (KOR) in the rostral ventromedial medulla (RVM) of male and female rats. This area is an important relay point in the transmission of pain sensation. KOR was found both pre-and postsynaptically on unmyelinated axons, axon terminals, dendrites, and somata. Specifically, the distribution of these receptors on dendrites in the neurons of the RVM was lower in proestrus females compared with estrus females, and they were less abundant in males. Findings suggest that sex hormones may regulate the distribution of these receptors and that the balance between pre- and postsynaptic sites may govern the different responses to analgesic treatments in males and females.

Serotonin, Migraine Headache, and the Menstrual Cycle

Research has sought to determine if serotonin levels play a role in migraine headache associated with the menstrual cycle. NIDCR-funded investigators are examining changes in serotonin metabolism in trigeminal ganglia of normally cycling female rodents. A variety of biological techniques were used to measure gene and protein levels, microscopy to localize specific types of neurons expressing serotonin receptors and metabolic enzymes, and cell cultures to examine the effects of estrogen on trigeminal neurons in vitro. Findings show that messenger RNA and protein levels of the rate limiting enzyme for serotonin production (tryptophan hydroxylase) were elevated in trigeminal neurons during proestrus when estrogen levels are highest. Interestingly, the levels of this enzyme were not regulated by estrogen in cell culture of these neurons nor were two receptors for serotonin, 5HT-1B and 5HT-1D. Serotonin was present in all nociceptive neurons of the trigeminal ganglia and co-localized with 5HT-1B receptors. These results suggest that this receptor may be an autoreceptor for serotonin and that changes in serotonin levels may contribute to menstrual migraine.

Gender Differences in the Release of Neurotransmitters

Research has looked at the release of amino acid neurotransmitters from the trigeminal caudalis/cervical cord junction in males, intact females, and ovariectomized females receiving low- or high-dose estrogen under acute inflammatory conditions. Males released glutamate, serine, and aspartate at five minutes and 45 minutes after injection of an inflammatory agent into the temporomandibular joint. Intact and ovariectomized females receiving a low dose of estrogen released these amino acids at five but not 45 minutes after injection while ovariectomized females receiving high estrogen exhibited no increase in amino acid release at any time point. The injection of a glutamate/aspartate reuptake inhibitor led to an elevation of glutamate levels in the trigeminal brainstem after inflammatory stimulation. The results suggest that sex hormone status may differentially affect glutamate neurotransmission in the trigeminal brainstem by altering glutamate reuptake after sensory input from the temporomandibular region.

Gender, Adolescent Development, and Pain

NIDCR-supported research has assessed the relationship of TMJD pain, abdominal pain, migraine and tension-type headaches, back pain, and multiple pain conditions to gender and pubertal development in a cross-sectional, population-based survey of more than 3,000 adolescents. The investigators also examined the association between pubertal development and depressive and somatic symptoms, factors often associated with persisting pain conditions occurring in adults. Study participants between 11 and 17 years old were randomly selected from databases maintained in a large

health maintenance organization. Adolescents reported on the presence of each pain condition in the prior three months and completed scales assessing pubertal development and depressive and somatic symptoms. The prevalence for back pain, headache, and TMJD pain was found to increase significantly with increasing pubertal development in girls, but only back pain increased significantly in boys. Rates of somatization, depression, and the probability of experiencing multiple pains also increased significantly with pubertal development in girls but not boys. Pubertal development was a better predictor of pain than was age for girls.

Sex Hormones and TMJD Pain in Pregnancy

Research has assessed the relationship between sex hormones and TMJD pain, the course of reported TMJD pain, and other TMJD signs and symptoms in pregnant women with musculoskeletal orofacial pain and pain-free comparison subjects. Participants were recruited during the first trimester of pregnancy. Patients completed questionnaires assessing pain, depressive and somatic symptoms, and underwent standardized TMJD examinations during the third, sixth, and ninth month of pregnancy, and one year postpartum. For the subjects meeting the criteria for TMJD, musculoskeletal orofacial pain diminished significantly during the second and third trimester of pregnancy and increased again at postpartum examination. As expected, study participants meeting the diagnostic criteria for TMJD showed higher levels of pain when facial muscles were palpated, diminished mandibular range of motion, and higher levels of psychological distress when compared with subjects without TMJD. However, among TMJD patients, marked objective improvements in TMJD symptom status during pregnancy were not accompanied by fully comparable levels of improvement in psychological distress. The investigators conclude that significant improvements in TMJD pain status occur during pregnancy; the improvements are most likely associated with the dramatic hormonal changes that occur during pregnancy.

Genes and Pain

Genetic studies on the area of pain include the haplotype mapping of catechol-O-methyltransferase (COMT) and responses to specific pain-evoking stimuli. Three common haplotypes in the COMT gene have been identified, and they relate to the threshold and tolerance to thermal, ischemic, and mechanical stimuli, as well as temporal summation to heat pain. The study included 202 females. Haplotype associations were strongest for measures of thermal pain, and there was no association of haplotypes and summation of heat pain. Interestingly, the val158met single nucleotide polymorphism (SNP) was associated with the summation of heat pain but not with other pain measures. The researchers propose a mechanism whereby the val158met SNP is important in the variation associated with pain summation while the other SNPs/haplotypes influence initial responsiveness to painful stimuli.

Temporomandibular Joint and Muscle Disorders

Temporomandibular Joint and Muscle Disorders (TMJD) are important chronic pain conditions of particular interest to the NIDCR. The following are examples of NIDCR-supported basic and clinical research on TMJD:

Integrins and Neural Activity

A study examined the effects of blocking integrins in the temporomandibular joint (TMJ) of male and female rats. Neural activity was measured in two areas of the trigeminal brainstem in response to jaw movement in the presence and absence of TMJ inflammation. Integrin antagonists significantly reduced neuron activation in the trigeminal caudalis/cervical cord junction in ovariectomized female rats when compared with males, independent of the inflammatory state of the animals. However, the same integrin antagonist did not alter neuron activation in response to jaw movement in the trigeminal interpolaris/caudalis junction of either male or female rats nor did it affect neuron activation after injection of inflammatory agent alone in the absence of jaw movement. These results suggest that integrins contribute to trigeminal activation by jaw movement only in the caudalis/cervical cord junction in a sex-dependent manner.

Genes and TMJD

Researchers have looked at common haplotypes in the beta-2-adrenergic receptor (ADRB2) and the role that they play in defining physiological and psychological phenotypes associated with painful TMJD. They have determined the ADRB2 haplotype of 202 females and examined the relationship among three common haplotypes and psychological factors, blood pressure, and the development of TMJD. They found that the haplotypes influence receptor expression levels and the efficiency of internalization after stimulation by agonists. The presence of haplotypes associated with the most positive psychological traits and higher resting blood pressure were also associated with a large reduction in the risk for developing TMJD. However, the relationship of the haplotypes and the psychological and cardiovascular phenotypes is complex and will require further study on larger populations.

TMJ Implant Registry and Repository

The NIDCR sponsored the development of the TMJ Implant Registry and Repository (TIRR) at the University of Minnesota. The aim of creating the TIRR was to understand the pathology of TMJD and provide information for the development of new TMJ implants. The TIRR has recruited and registered 63 TMJ surgeons and specialists from all parts of the U.S. who, in turn, recruit subjects for the TIRR. At the present time, 94 patients with a history of TMJ alloplastic implants are enrolled in the registry. A national recruitment effort is ongoing. Additional information is available on the registry's Web site at http://tmjregistry.org.

OPPERA

A seven-year clinical study could accelerate research on better pain-controlling treatments for TMJDs. This study, the Orofacial Pain: Prospective Evaluation and Risk Assessment or OPPERA, marks the first, large, prospective clinical study to identify risk factors that contribute to the development of TMJ disorder. During the OPPERA study, scientists will track 3,200 healthy volunteers from three to five years to see how many develop the disorder. The multicenter research program will involve investigative units at the University of Florida in Gainesville, University of Buffalo-SUNY, University of Maryland at Baltimore, and University of North Carolina, Chapel Hill.

Diagnosing TMJD

Researchers tested and improved the reliability and validity of the widely used research diagnostic criteria (RDC) for TMJD. In this study, investigators found that more than one-fourth of clinically normal subjects, with no lifetime history of TMJD symptoms, received TMJ imaging readings indicative of TMJ disc displacement. The proportion of positive MRI readings for disc displacement in pain history-negative subjects was not significantly different from the proportion of positive MRI findings among pain history-positive subjects. The authors conclude that MRI findings indicating disc displacement are quite common and not significantly associated with a history of jaw pain, at least viewed from a cross-sectional vs. longitudinal perspective. These same investigators have also developed and tested modifications to the RDC for TMJD, which improve its sensitivity and specificity for the most prevalent types of TMJDs.

Other TMJD projects specific to bioengineering and cell regenerations include those on the characterization of the TMJ disk at cellular and tissue levels. This research would be used for engineering in vitro TMJ disc prototypes that approximate native disc structure and function. Other studies in these areas include the development of stem cell-based approaches for regeneration of TMJ, the optimization of the stiffness and porosity of the TMJ scaffolds to enhance TMJ bone regeneration, and the contribution of mechanical stress and loading to properties of the TMJ scaffolds.

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. The focus on bone and other mineralized tissues is appropriate not only because of their importance as they relate to teeth and jaws, but also because they relate 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 resorp-

tion 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 bone (less than 20 years old), bone formation dominates resorption, resulting in bone growth and development. In healthy adult bone (20 to 40 years old), the processes of bone formation and resorption are delicately equilibrated, with no increase or decrease in bone mass occurring. 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.

The following are examples of NIDCR-supported studies on bone mineralization.

Mouse Model to Study Disruption of Dentin Matrix Protein

Scientists developed a mouse model with targeted disruption of dentin matrix protein 1 (DMP1) to study the in vivo function of the molecule. DMP1 is expressed exclusively in the bone and dentin. These knockout animals have an overall decrease in bone mineral content. They have thinner cortical bone volume and lower calcium and phosphate ionic concentration. The size and quality of the minerals were also compromised. However, the formation of bone matrix was unaffected. Data from this study support a significant and specific role for DMP1 in the regulation of bone mineralization.

Bone Morphogenetic Proteins and Runx2

Investigators have addressed a gap in scientific information as to how bone morphogenetic proteins (BMPs), a family of pleiotropic proteins, direct their highly specific osteoinductive function to regulate Runx2. A series of publications demonstrate the extensive signaling network, at the level of growth and transcription factor interaction, engaged by BMPs in regulating bone formation. As a proof of principle, fibroblasts were engineered to deliver combinations of BMPs in an implantation model in which specific cooperative molecular interactions enhanced bone repair. These studies illuminate the physiology of bone repair and strategies for the optimization of bone augmentation. More importantly, these studies are examples of the successful translation of basic science discoveries into clinical utility.

TIEG and Bone Homeostasis

NIDCR research has looked at the generation of the transforming growth factor beta (TGF-b) inducible early gene-1 (TIEG) knockout mouse model and the characterization of the phenotype. These animals were osteopenic with decreased cortical and trabecular bone volume, decreased bone mineral density, and weaker bones that were susceptible to fractures. Consistent with in vitro data, these new in vivo results support the significant role of TIEG in bone homeostasis. Future investigations will focus on how TIEG interacts with many other factors also known to regulate bone growth.

In addition, the NIDCR has supported studies that may be of importance for therapeutic interventions that control bone loss in periodontal diseases and osteoporosis. One study designed an inhibitory peptide WP9QY that competitively binds to and titrates the amount of RANK ligand. Thus, it demonstrated that WP9QY inhibited RANK ligand-induced osteoclast formation and bone resorption both in vitro and in vivo. Another study aimed to identify regulatory elements residing in the promoter sequence of human osteoclast inhibitory peptide-1 (OIP-1). Significantly, a Stat-1 binding site was pinpointed and further characterized to be responsive to interferon gamma. The identification of this regulatory pathway of OIP-1 provides molecular targets that could be used to modulate osteoclast activities.

Autoimmune Disease

Autoimmune disorders disproportionately affect women and result in the unintended destruction of the body's own tissues. In the oral cavity, autoimmune disorders include Sjögren's syndrome (SS), 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 U.S. and is estimated to affect one to two million people, with a female-to-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.

NIDCR intramural researchers are studying the natural history and immunopathogenensis of SS. Regarding the natural history, a study of men and women with SS matched by age and race showed no difference between the two genders in clinical manifestations and objective severity in oral and ocular finding, but women reported significantly more subjective discomfort. Another study is looking at the treatment of SS with tumor necrosis factor (TNF) inhibitors, which are effective in multiple other autoimmune diseases. This study started by defining the underlying immunological parameters associated with SS before and after treatment with TNF inhibitors. Among the cytokines elevated in the blood in SS patients and connected to SS in diseased salivary gland tissue is interleukin 17, a new cytokine linked with chronic inflammation and autoimmunity. Several additional cytokines have been shown to be supporting molecules for the development of a new lineage of IL-17 secreting lymphocytes, the CD4+ T helper lymphocyte lineage 17 (Th17). These supporting cytokines are also present and correlate with salivary gland focus scores, an indicator of degree of disease. Additionally, a type I interferon pathway can be linked to SS as shown in collaborations with investigators at the Hospital for Special Surgery in New York and investigators in Athens, Greece. In this study, treatment with anti-TNF agents results in significantly increased interferon, consistent with the failure of TNF antagonists to suppress disease. As the intramural researchers further characterize these potential TNF-independent molecular pathways of autoimmune glandular tissue damage, it is anticipated that new and more specific treatment strategies may emerge for SS.

In addition, the NIDCR funded the establishment of an International Research Registry Network for Sjögren's Syndrome with the purpose of: (1) setting standardized diagnostic criteria for the diagnosis for SS; (2) collecting, processing, storing, shipping, and analyzing clinical and biological specimens from patients and families with SS; and (3) disseminating to researchers clinical information and biological specimens from patients with SS and their families. As of October 3, 2006, 642 subjects have been enrolled and have completed baseline examinations. In addition, 595 sets of specimens (including tissue, blood, saliva, and tears) have been stored for future studies.

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, including difficulty in swallowing, chewing, and speaking as well as loss of enjoyment of food. Lack of saliva also increases oral diseases, such as dental caries, periodontal diseases, and other infections, incurs nutritional deficiencies, and reduces the quality of life. Many diseases and conditions can induce salivary gland hypofunction, such as SS and rheumatoid arthritis. NIDCR scientists are conducting animal studies, using the female non-obese diabetic (NOD) mouse as a model for the autoimmune sialadenitis occurring in SS. NOD mice develop spontaneous autoimmune sialadenitis and loss of salivary flow that is age and gender dependent. The NOD model was used to evaluate if transfer of the vasoactive intestinal peptide (VIP) cDNA could be useful in management of SS. A previous hypothesis has postulated that VIP, which has immune, secretogogue, and trophic activities, might be useful to reduce the autoimmune reactivity in SS. A serotype 2 AAV vector encoding the human VIP transgene (rAAV2hVIP) was constructed and administered to submandibular glands prior to the onset of the autoimmune sialadenitis. Findings suggest that rAAV2hVIP led to significantly improved salivary flow rates and a reduction of several cytokines in salivary gland extracts [IL-2, IL-10, IL-12 (p70), and TNF-alpha], as well as serum RANTES (regulated on activation normal T expressed and secreted cytokine), compared with results seen with a control AAV2 vector. However, investigators did not detect any differences in lymphocytic infiltrates (focus scores) in the glands.

Human Immunodeficiency Virus (HIV)

The study of the oral manifestations of HIV infection has been of great interest to the NIDCR because oral lesions in HIV-infected individuals are frequent and varied, and they are among the first symptoms of infection. The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic. The component of one NIDCR training grant is an oral study of HIV-posi-

tive women in Zimbabwe with the following goals: (1) to estimate oral disease incidence in relation to CD4 count while controlling for potential confounders, such as current sexually transmitted diseases; and (2) to estimate the sensitivity and specificity of visual inspection by trained nurses to detect oral mucosal lesions in patients in family planning/gynecology clinics in Harare, Zimbabwe. As of the last progress report, 581 women have been enrolled in the study. Oral candidiasis was the most common lesion diagnosed by the oral surgeon and by nurses, and oral candidiasis was strongly associated with a low CD4 count. The agreement rate between the nurses' and the oral surgeon's examinations was high (greater than 90 percent). In conclusion, pseudomembranous candidiasis may be used as a surrogate marker of disease progression and is reliably diagnosed by nurses.

Initiatives

Request for Applications (RFAs)

- **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)
- **The Role of Neuronal/Glial Cell Interactions in Orofacial Pain Disorders**
  The goal of this initiative is to stimulate basic research on the role of glial cells in pain disorders of the orofacial complex and, in particular, studies on the interactions between glial cells and neurons that lead to pathological pain states. This initiative will encourage molecular, cellular, and animal studies on: (1) the mechanisms by which stimulation of primary afferent nociceptors (neurons) lead to activation of spinal cord, brain, and peripheral glial cells; (2) the influence of activated glial cells (astrocytes and microglia) on nociceptive neuron function in experimental pain models; (3) the identification of glial cell proteins and signaling pathways important in maintaining chronic pain states; (4) the identification of the neuronal proteins and signaling systems regulated by activated glial cells; and (5) the role of activated microglia as antigen presenting cells influencing systemic immune cell interactions with the CNS. (RFA-DE-06-005)
- **Sjögren's Syndrome: A Model Complex Disease**
  The focus of this RFA is to use an integrated approach to elucidate the mechanisms and processes underlying the complexity of SS, an autoimmune disease prevalent in women. Integrative, multidisciplinary research approaches are encouraged to address the gaps in scientific and clinical knowledge, provide more precise molecular understanding of the pathophysiology of SS, and develop preventive measures and therapies for this syndrome. (RFA-DE-06-004)
- **Health Promotion Research Directed to Improving the Oral Health of Women and Their Infants**
  The purpose of this RFA is to support health promotion research directed at women before, during, and after pregnancy to improve their health and well-being as well as that of their infants. (RFA-DE-06-008)

Program Announcements (PAs)

- **Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Comorbid Conditions**
  The purpose of this program announcement is to stimulate research to discover etiological and pathophysiological mechanisms underlying a set of chronic, comorbid conditions associated with TMJDs. (PA-06-188)
- **Pathophysiology of Bisphosphonates-associated Osteonecrosis of the Jaw**
  The goal of these program announcements, which support research through three different mechanisms (R01, R21, and R03), is to identify and characterize the pathophysiological mechanisms that lead to impaired bone healing and the development of osteonecrosis of the jaw (ONJ). (PA-06-500; PA-06-501; PA-06-502)

- **Clinical Studies of Bisphosphonate Therapy and Osteonecrosis of the Jaw**
  The goal of this program announcement is to explore the association between ONJ and bisphosphonate therapy. (PA-06-556; PA-07-185)

Conferences and Workshops

- **Craniofacial Skeletal Tissue Engineering Conference**
  The NIDCR supported a conference titled Developmental Defects of the Craniofacial Skeleton: From Genetics to Therapies. The program of the meeting included a broad spectrum of highly qualified speakers who presented talks in areas ranging from cell signaling and mechanisms of teratogenesis to surgical therapies of various craniofacial skeletal defects, including TMJD. This conference exposed scientists and clinicians to new strategies of diagnosis and treatment of craniofacial skeletal disorders, including TMJDs.
- **8th International Conference on the Chemistry and Biology of Mineralized Tissues**
  This conference brought together investigators who presented the state-of-the-science in mineralized tissue research.
- **3rd International Women's Leadership Conference for Education, Research and Service, under the leadership of the American Dental Education Association**
  The theme for this conference was Global Health through Women's Leadership. The nine topics selected for the conference were: (1) global issues in dental and oral health related to systemic health; (2) advancement of women in academic and research careers and in professional societies; (3) mentoring, role modeling, and networking; (4) clinical relevance of gender and oral health (including the women's HIV study); (5) gender generation gap: women as agents for organizational change; (6) work-related issues: time management and leadership in the office; (7) entry into dentistry through different career pathways; (8) alternative medicine, women's health, and keeping women fit; and (9) re-entry: engineering career development. Both the NIDCR and the NIH ORWH were co-sponsors of this conference.
- **Gordon Research Conference on Bones and Teeth**
  The conference brought together investigators to discuss late-breaking discoveries in mineralized tissue biology, including growth and transcription factor regulation, mineral homeostasis and calcification, skeletal anabolic agents, and stem cells.
- **Workshop on Sjögren's Syndrome: Transition from Autoimmunity to Lymphoma**
  This workshop fostered the exchange of scientific data and catalyzed rigorous discussion about potential triggers in the transition from autoimmunity to lymphoma.
- **Advances in Pain Research**
  The purpose of this symposium was to highlight recent advances in pain research conducted by NIH-supported investigators. A broad range of topics was presented, describing basic and clinical research of interest to the NIH pain community.
- **Fourth Temporomandibular Joint Association Scientific Meeting**
  This meeting, A Systems Approach to the Understanding of TMJ as a Complex Disease, focused on medical conditions and other health problems that TMJ patients often report in addition to their TMJ symptoms. In addition, the meeting aimed to develop strategies for an integrated approach to research on TMJD that take into consideration other conditions; encourage interdisciplinary research in this field; and provide a forum for discussion among TMJ patients, senior investigators, junior faculty members, and graduate students.

Health Disparities among Special Populations of Women

The NIDCR's strategic plan includes a goal to eliminate 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 were jointly funded with the NCMHD, 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 during the prenatal period in combination with fluoride varnish use with the infants. Both the test and control groups of mothers receive oral disease prevention counseling. In another randomized clinical trial, 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 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.

Other NIDCR-supported investigators have initiated policy-related research on the association between low-income mothers' use of dental care and their children's oral health status. The investigators aimed to evaluate whether mothers having a regular source of dental care (RSDC) could potentially produce oral health benefits that accrued to both the mother and child. Medicaid-eligible children between the ages of three and six years were identified from a statewide database, and a stratified sample in four racial/ethnic groups was selected. The mothers were contacted by phone to respond to a survey assessing mothers' RSDC, personal and family characteristics, self-rated dental health, number of dental problems, flossing frequency, and beliefs that cleaning prevents cavities and loose teeth. About 39 percent of the mothers reported having a regular place of dental care or dentist. Across racial/ethnic groups, having a RSDC was associated with better oral health for all measures, greater likelihood of a dental cleaning and less likelihood of tooth extraction, and positive beliefs regarding flossing. Dental utilization records for the Medicaid-eligible children and indices of the children's oral health status are still being collected. In addition, a female researcher with a career development grant is looking at the contribution of individual-level risk factors, such as age, gender, diabetes, smoking, and time since last dental visit, to socioeconomic and racial/ethnic differences in periodontal health. The analysis was repeated and evaluated for changes between NHANES III and NHANES 1999-2000. Findings indicated that race/ethnicity, education, and neighborhood SES conditions were associated with increased odds of having periodontitis in NHANES III.

Craniofacial Anomalies

Clefts of the lip and palate are common human birth defects of multifactorial etiology, and approximately 70 percent are non-syndromic. The Oral Cleft Prevention Program, being supported by the NIDCR, is part of the NICHD's Global Network for Women's and Children's Health Research. The specific aim of this program is to reduce the recurrence of non-syndromic cleft lip and/or palate in a high-risk group of women through supplementation with folic acid at preconception and throughout the first three 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.

Periodontal and Other Diseases

Several studies have suggested a significant association between maternal periodontal disease and pregnancy complications that result in preterm delivery (i.e., gestational age of less than 37 weeks) and decreased fetal weight (i.e., birth weight of less than 2500g). Maternal periodontal infections may potentially represent a bona fide risk factor for preterm birth and growth restriction. Other evidence suggests that periodontal disease and its progression may represent an infectious and inflammatory exposure that could have serious deleterious effects during pregnancy.

The NIDCR sponsored two large randomized trials designed to determine if non-surgical treatment of periodontal disease during pregnancy could reduce the incidence of preterm birth and associated growth restriction. Non-surgical, or standard, periodontal treatment involves thoroughly cleaning the teeth above and below the gums and is commonly called scaling and root planning.

Both the Obstetrics and Periodontal Therapy (OPT) Trial and the Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) Trial were designed to determine whether pregnant women having non-surgical periodontal therapy during the second trimester of pregnancy had fewer premature and/or low-birth weight infants when compared with women having periodontal therapy delayed until after delivery. Results from the OPT trial were published recently in the New England Journal of Medicine. Findings indicated that pregnant women who received non-surgical treatment for their periodontal disease during the second trimester did not significantly lower their risk of delivering a premature or low birth-weight baby. This study also evaluated the safety of general dental care during pregnancy. It found that dental treatment through the second trimester—both general and periodontal care—did not increase the number of adverse events for women during pregnancy.

The MOTOR Trial is still active and is expected to be completed by FY 2008. Total enrollment will be 1800 subjects. Investigators have reported progress in the trial for the fiscal years of this report. In FY 2005, the second year of the project, 1982 potential participants were screened, and 285 subjects were randomized. The total number of randomized subjects for the entire project through FY 2005 was 308 persons. In FY 2006, MOTOR investigators screened a total of 2,740 potential participants and randomized a total of 542. For the entire project, including years one to three, a total of 5,524 participants were screened, and 888 of those were randomized.

The MOTOR steering committee has monthly conference calls. These calls have facilitated monitoring activities and decision making with regard to the study. Continued calibration and recalibration of dental examiners was performed in year three.

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 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; painful bladder syndrome/interstitial cystitis (PBS/IC); urinary tract infections (UTIs); urinary incontinence; and lupus nephritis, the kidney disease of systemic lupus erythematosus. Areas of the NIDDK mission also may have an important impact on diseases that are primarily within the mission of other ICs, such as hormonal factors in breast cancer and the relationship of obesity to cardiovascular disease (CVD). 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 2005 and 2006, 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; irritable bowel syndrome and other functional gastrointestinal disorders; liver disease research; obesity and nutrition; kidney disease; PBS/IC; urinary tract infections; and urinary incontinence. The ORWH has worked with the NIDDK to foster research in many of these areas.

Accomplishments

Diabetes

An estimated 20.8 million Americans, including 9.7 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, older women, and women who are members of racial/ethnic minorities in the U.S. are at significantly increased risk of developing type 2 diabetes.# The NIDDK supports numerous 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 NIDDK, together with the CDC, also supports the National Diabetes Education Program (NDEP). The NDEP 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 following highlights of NIDDK-supported diabetes research are particularly relevant to women's health.

Type 2 Diabetes—Susceptibility and Sex Differences

Understanding the biologic basis for susceptibility to type 2 diabetes includes understanding differences in risk factors and disease development in women and men. For example, insulin resistance is a sign of increased risk of type 2 diabetes, and a number of NIDDK-supported research studies are examining the mechanisms by which estrogen may ameliorate insulin resistance; the ORWH has helped foster this research. One newly funded study, co-supported by the ORWH, will use animal models to better define the causes and effects of hormone signal cross-talk between estrogen and other hormones involved in the regulation of insulin sensitivity. The study may help to advance our understanding of how hormone signal cross-talk and how sex differences in these responses may affect both type 2 diabetes and obesity. NIDDK-supported researchers have also conducted a systematic review and meta-analysis of clinical study data aimed at comprehensively assessing the relationships between levels of endogenous sex hormones and risk of type 2 diabetes to sort out conflicting or inconsistent data in this area. Their analysis indicates that endogenous sex hormones may differentially modulate glycemic status and diabetes risk in women and men. In particular, high testosterone levels were associated with greater type 2 diabetes risk in women but lower risk in men. This report will help inform future studies.

Environmental Factors Contributing to Type 2 Diabetes Risk in Women

Scientists are teasing out how dietary and other environmental factors contribute to metabolic disorders, such as type 2 diabetes. NIDDK-supported researchers studying the "metabolic syndrome," which is a constellation of risk factors for type 2 diabetes, recently found an inverse correlation between magnesium intake and both systemic inflammation (as measured by the biomarker, CRP) and the prevalence of the metabolic syndrome in women. This study was conducted among participants in the Women's Health Study, a cohort of mostly white women 45 years of age and older, initially free of CVD and cancer. Another research team found a similar inverse correlation between a diet high in magnesium-rich foods and risk of type 2 diabetes among participants in the Black Women's Health Study. This research came out of a newly funded research project grant, the goal of which is to use this large prospective cohort to examine diabetes risk factors specific to black women.

Continued Benefits to Preventing or Delaying Type 2 Diabetes

According to recent estimates, at least 54 million Americans have "prediabetes," a condition of impaired glucose metabolism that identifies them as at high risk for developing type 2 diabetes. Researchers are continuing to gain new insights from the Diabetes Prevention Program (DPP), a clinical trial that examined the effects of lifestyle and medical interventions on the development of type 2 diabetes in adults at risk for this disease. The DPP compared intensive lifestyle modification, treatment with the drug metformin, and standard medical advice. Published in 2002,

the DPP results showed that participants who received the lifestyle intervention had a dramatically reduced risk (by 58 percent) of developing type 2 diabetes. Metformin reduced diabetes risk by 31 percent. Sixty-eight percent of the DPP study participants were women. The ORWH provided support for the DPP, which facilitated recruitment and retention of women with a history of gestational diabetes (13 percent of all female participants). The NDEP's Small Steps. Big Rewards. Prevent Type 2 Diabetes education campaign is continuing to translate the results of the DPP into practical health information for the public. Importantly, steps taken to prevent or delay type 2 diabetes can also apparently help reduce risk factors for diabetes complications, such as CVD. New data analyses of the DPP show that hypertension, a classic risk factor for CVD, was present in about 30 percent of all participants at the beginning of the study and increased in the patients who received either placebo or metformin. However, hypertension significantly decreased in the lifestyle intervention group. Levels of recently identified, non-traditional risk factors for CVD—such as C-reactive protein and fibrinogen—were lower in the metformin and lifestyle groups, with a larger reduction seen in the lifestyle group. About half of all DPP participants had a condition known as the metabolic syndrome, which is defined by the presence of several conditions that increase risk for the development of type 2 diabetes and CVD. Both lifestyle modification and metformin therapy reduced the development of the metabolic syndrome, with lifestyle modification more effective. An ongoing study is examining longer-term effects of the trial interventions on the prevention of type 2 diabetes and its cardiovascular complications in DPP participants. This study, the DPP Outcomes Study (DPPOS), will also compare outcomes for women and men, and by age and ethnicity. The DPPOS is co-supported by the ORWH. In another effort, a newly funded exploratory project, co-funded by the ORWH, will examine the metabolic impact of lactation in young mothers to better understand how lactation may reduce diabetes risk factors in these women.

Gestational Diabetes and Diabetes Prevention

Women can develop a reversible state of diabetes during pregnancy called gestational diabetes (GDM). GDM affects about 7 percent of U.S. pregnancies annually, increasing risk of complications during pregnancy and birth for both mother and fetus. Women who have had GDM have a 20 to 50 percent chance of developing type 2 diabetes within the next five to 10 years following pregnancy. GDM occurs more frequently among obese women and women with a family history of diabetes. It is also more frequent among African American, Hispanic/Latina, American Indian, and Alaska Native women—women in minority groups already at disproportionately high risk for type 2 diabetes. The children of women with a history of GDM are also at an increased risk for obesity and diabetes compared with other children. Encouragingly, the DPP study showed type 2 diabetes can be prevented or delayed in people at risk, including women with a history of GDM. To help women with a history of GDM prevent or delay type 2 diabetes and to help their children lower their risk for the disease, the NDEP launched a campaign tailored for this audience in the spring of 2006, titled It's Never Too Early to Prevent Diabetes. This campaign is part of the Small Steps. Big Rewards. Prevent Type 2 Diabetes campaign, and it is providing health information materials in both English and Spanish for women and their families. (See section below on Minority Health Disparities for further information.) New GDM research studies that are underway include projects testing interventions specifically to prevent type 2 diabetes in women with GDM; a study examining basic mechanisms underlying GDM that could pave the way to a new intervention; a study co-funded by the ORWH to identify potential biomarkers for the development of GDM and preeclampsia, thus enabling earlier intervention; a study to improve diabetes management and pregnancy outcomes for women with GDM; and study of primary prevention of GDM. Several new and ongoing projects focus on reducing the burden of GDM in minority or underserved women. In an encouraging advance, one research team recently published results indicating that treatment with a

particular class of insulin-sensitizing drugs (thiazolenediones) protects beta cell function and delays progression to type 2 diabetes in Hispanic women with prior GDM. The Pioglitazone in Prevention of Diabetes (PIPOD) study was built on a prior study in this cohort (the TRIPOD study), which showed that treatment with the drug troglitazone stabilized beta-cell function; it also showed that there was a strong relationship between an initial reduction in insulin output during treatment and the risk of diabetes. (Troglitazone was withdrawn from clinical use in 2000.) Because similar results have now been obtained with pioglitazone, it appears that treatment with this class of insulin-sensitizing drug may be an important strategy to help prevent or delay type 2 diabetes in these women at high risk. Another study from this research group suggests that use of injectable progestin (DMPA) hormonal contraceptive can interact with other metabolic risk factors to further enhance diabetes risk in Hispanic women with prior GDM. This finding suggests further areas of study to fully flesh out type 2 diabetes risk factors in women already at high risk.

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. 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 recently launched the multicenter HEALTHY study. HEALTHY is designed to target food service and physical education changes in schools and to promote healthy habits, in hopes of lowering risk factors for type 2 diabetes in middle school students. This prevention trial is being conducted at sites across the country. A multisite trial of treatment strategies for girls and boys already affected by type 2 diabetes is ongoing.

Progress in Preventing Cardiovascular Complications in People with Diabetes

CVD is the leading cause of death in patients with diabetes. The risk of death due to heart disease is increased two- to four-fold in all patients with diabetes when compared with their age-matched non-diabetic counterparts. In women, the risk elevation is even greater (four- to six-fold). The Epidemiology of Diabetes Interventions and Complications (EDIC) is a long-term followup study to the Diabetes Control and Complications Trial, which demonstrated that intensive control of blood sugar levels reduces the risk of eye, nerve, and kidney complications in type 1 diabetes patients. Now, recent results have shown that intensive control of blood sugar levels in the DCCT also lowered the risk of heart disease and stroke by 50 percent in participants during the average 17 years of patient follow up (DCCT and EDIC combined). The NIDDK is co-supporting the NHLBI-led Action to Control Cardiovascular Disease Risk in Diabetes (ACCORD) trial, which is expected to provide similar insights regarding blood sugar control and CVD risk in patients with type 2 diabetes. Another clinical trial addressing CVD and diabetes that may prove especially beneficial for women is the LookAHEAD (Action for Health in Diabetes) clinical trial. This multicenter trial in more than 5,100 participants (nearly 60 percent women) is underway 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 CDC.

Diabetes and Risk of Bone Fracture

Diabetes complications are not limited to major organ systems. Mounting evidence suggests that diabetes also affects risk of bone fracture in women. One recent study by NIDDK-supported researchers examined whether middle-aged premenopausal women with type 1 diabetes had more self-reported fractures and lower bone mineral density than nondiabetic counterparts. They found that the diabetic women were more likely to report fractures after age 20. They also had a 3 to 8 percent lower bone mineral density in the total hip, femoral neck, and whole body than nondiabetic women, after adjustment for potential confounding factors.

Although the mechanism remains elusive, the study indicates that type 1 diabetes enhances the already greater risk of fracture in this age group. Similarly, a prospective study of hip fracture among nearly 110,000 women participating in the Nurses' Health Study found that, after adjusting for other factors, type 1 diabetes conferred a 6.4-fold greater relative risk of hip fracture, and type 2 diabetes conferred a 2.2-fold greater relative risk of hip fracture during the 22 year follow up period. These studies suggest that diabetes status in women should be considered in osteoporosis screening and fracture prevention strategies.

Genetic Markers of Diabetes Susceptibility

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. In a recent advance, NIDDK-supported researchers capitalized on data available from the DPP to study the effect of a diabetes susceptibility gene identified by industry. They confirmed in the large and ethnically and racially diverse DPP cohort that specific variants in the TCF7L2 gene predispose people to type 2 diabetes. Importantly, this study revealed that individuals at high risk due to the gene variant still benefited from the intensive lifestyle and metformin interventions in the DPP that successfully delayed or prevented type 2 diabetes. 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. 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. Finally, a newly funded study will utilize the large, international Hyperglycemia and Adverse Pregnancy Outcome cohort to define genetic factors that specifically influence maternal glycemia and birth weight, which in turn affect diabetes risk in offspring and maternal health risks during pregnancy.

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 or predominantly affecting women, such as thyroid diseases (including Graves disease, goiter, and hypothyroidism), hyperparathyroidism, breast cancer, and osteoporosis.

Nuclear Receptor Signaling Atlas

Many endocrine diseases evolve from disruption of normal patterns of signal transduction and control of gene expression by members of the nuclear receptor superfamily, such as sex steroid hormone receptors. Research on these diseases is benefiting from the Nuclear Receptor Signaling Atlas (NURSA), a consortium supported by the NIDDK, the NCI, and the NIA that is designed to develop, collate, and distribute information about nuclear receptor and coregulator structure, function, and role in disease. While much is known about many individual nuclear receptors in specific target tissues, less is known about global patterns of nuclear receptor activity. In recent studies, NURSA researchers used a systems biology approach to interrogate nuclear receptor expression in mouse tissues. In one study, the researchers uncovered critical new information about relationships between various nuclear receptors, elucidating similarities and hierarchical relationships in their expression. This research suggests the existence of a higher order transcriptional network that extends beyond individual tissues and may help govern physiology of the entire organism. In a complementary study, researchers examined nuclear receptor expression at multiple time points in key metabolically active tissues and found that many were expressed in a rhythmic cycle. These findings suggest that the nuclear receptors may help link the circadian clock and metabolism. These studies significantly advance researchers understanding of nuclear receptor relationships and roles, and they provide tools for additional research on the biological roles of both individual nuclear receptors and the receptors as a superfamily—including exploration of sex-based differences in these roles.

Gene Regulation in Breast Cancer

Much of NIDDK-supported breast cancer research focuses on hormonal regulation of cellular growth and function by both steroid

hormones and growth factors. Many tumors that arise in epithelial cells, including breast tumors, result from an inappropriate response of a normal cell to hormones, growth factors, or cytokines. In breast cancer, cells may be particularly responsive to the hormone estrogen. Hormone-sensitive cancers may initially respond to treatments that capitalize on this sensitivity, but, in most instances, the tumor will eventually develop independence from hormone action and continue to thrive even when estrogen is removed or its action blocked. Researchers are intensively investigating the driver of gene expression in hormone-sensitive breast cancers—DNA binding by the estrogen receptor—in an effort to better understand these cancers. In a recent advance, NIDDK-supported researchers exhaustively mapped binding sites for the major estrogen receptor, estrogen receptor-alpha, throughout the genome. They identified a final set of 3,665 unique estrogen receptor binding sites. By combining this receptor map with gene expression data, they shed light on previously unexplored genomic regions that are important regulators of the estrogen dependence of breast cancer cells. They also identified other factors that cooperate with the estrogen receptor to influence estrogen signaling in breast cancer. These results provide an important new resource for study of gene regulation in breast cancer and the development of therapies targeting estrogen receptor action.

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 about 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. An important new advance suggests that simple estrogen deficiency is not the central cause of postmenopausal bone loss. When ovarian function declines at menopause, levels of the pituitary hormone, follicle-stimulating hormone (FSH), rise. Through experiments in animal models and in cell cultures, NIDDK-supported researchers have found evidence suggesting that FSH acts to induce bone loss in an estrogen independent manner. This study opens the way to exploring the relative contributions of pituitary and sex-steroid hormones to osteoporosis and may lead to novel approaches for preventing and treating this condition.

Digestive Diseases

The NIDDK supports a substantial portfolio of basic and clinical research on digestive diseases, a number of which disproportionately affect women. These include functional gastrointestinal disorders, such as irritable bowel syndrome (IBS) and fecal incontinence, and liver and biliary disorders, such as primary biliary cirrhosis. The following highlights of NIDDK-supported digestive diseases research are particularly relevant to women's health.

Advancing Digestive Diseases Research

To identify promising future research directions for digestive diseases, the NIH has established a National Commission on Digestive Diseases (NCDD). The NCDD is charged with developing a long-range research plan for the field. The NIDDK is leading NIH support for this effort. The NCDD will conduct an overview of the state-of-the-science in digestive diseases research and make specific recommendations to improve approaches to diagnosis, treatment, and prevention. The ORWH has joined the NCDD as an ex officio member and will help coordinate the NIH efforts to implement the research recommendations in the plan for IBS and other digestive diseases that disproportionately affect women. In another effort, the NIDDK and the NIH OMAR, with input from the ORWH and other NIH and HHS components, are planning a state-of-the-science conference on fecal and urinary incontinence to be held in 2007. Both urinary and fecal incontinence are more common in women than in men. This conference will help identify important research questions for the future.

Irritable Bowel Syndrome

The functional gastrointestinal disorder, IBS, causes pain and constipation or diarrhea, and it is especially common in women. While diet and stress contribute to this disorder, the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. People with IBS have a colon that seems to respond strongly to stimuli that would not bother most individuals. A key goal for research is to understand the interplay of gut and brain pathways in these disorders and to build upon this knowledge in designing effective treatments. Researchers have also been examining sex and gender differences in this interplay. For example, the autonomic nervous system (ANS) modulates and coordinates motility, secretion, and immune function in the gut and is a likely mediator of brain-gut interactions. A recent study reported that physical measures of ANS function differed between IBS patients and healthy controls subjected to a rectal stimulation (sigmoid balloon distention). These differences, however, appeared to be predominantly among the male IBS patients. In contrast, a study examining visceral perception of discomfort with rectal stimulation (sigmoid balloon distention) in patients with IBS or healthy controls found greater differences among women. Women with IBS had a significantly lower discomfort threshold than both men with IBS and healthy women, who were the least sensitive of all. However, women with or without IBS also showed a significant lowering of discomfort thresholds (increased sensitization) after repeated noxious rectosigmoid stimulation, while men did not. Both studies add to the growing body of knowledge regarding the importance of sex and gender differences in IBS and the implications for therapeutic approaches. These studies were conducted by researchers at a Specialized Center of Research for Women's Health at UCLA, co-funded by the NIDDK and the ORWH. This center 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.

Liver and Biliary Disease Research

Liver and biliary disease is an important cause of morbidity and mortality in the U.S. 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. A newly funded grant, which is co-funded by the ORWH, will investigate whether individual variability in patterns of random X chromosome inactivation in women plays a role in the autoimmune liver disease, primary biliary cirrhosis (PBC). Another newly funded project is investigating whether there are sex differences in the processes underlying gallstone formation that explain its greater prevalence in women. To further research on these and other liver and biliary diseases, the NIDDK is playing a leading role in promoting the implementation of the 2004 trans-NIH Action Plan for Liver Disease Research. This plan was developed under the auspices of the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee. It is based on input from a broad range of external investigators involved in liver disease research, staff of the NIH (including the ORWH), other Federal agencies, industry, health care providers, and concerned lay persons. Implementation efforts include a recent review of progress for the first year of the Action Plan and planned meetings at the five- and 10-year anniversaries of its publication to encourage public participation and input for realizing the Action Plan's goals.

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 66 percent of the U.S. adult population is overweight or obese, with approximately 32 percent meeting criteria for obesity. It is estimated that more than half of non-Hispanic African American women and more than 40 percent of Mexican American women are obese.# Obese individuals are at increased risk for numerous life-threaten-

ing 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, including nutrition, physical activity, epidemiology, behavioral intervention, surgery, neuroendocrinology, and fat cell biology. This research helps understand the underpinnings of obesity, including basic biological differences that predispose to sex/gender differences in fat accumulation and deposition. It will also determine how best to prevent obesity 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). The WIN provides health professionals and consumers with science-based information on obesity, weight control, and nutrition. (See section below on Minority Health Disparities for further information on WIN efforts.) Trans-NIH efforts in obesity research have been strengthened by the work of the NIH Task Force on Obesity. This task force is co-chaired by the NIDDK and NHLBI Directors; multiple NIH Institutes and Centers (ICs) and Offices, including the ORWH, are part of the Task Force. The Task Force spearheaded development of a trans-NIH strategic plan for NIH Obesity Research (2004) and continues to meet to discuss goals and report on implementation activities related to the plan. NIDDK 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. The following highlights of NIDDK-supported obesity and nutrition research are particularly relevant to women's health.

Preventing Weight Gain in Women

Epidemiological studies have indicated that specific stages of life, including adolescence, marriage, postpregnancy, and menopause, confer high risk for the development of obesity in susceptible individuals. Studies have also demonstrated a link between being 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 racial and ethnic groups in the U.S.); the ORWH is helping to foster this research. One newly funded study will test whether behavioral lifestyle intervention during pregnancy can reduce the number of normal weight and overweight women who exceed recommendations for pregnancy-related weight gain, with the goal of preventing long-term weight retention or gain postpartum. A new randomized clinical trial is testing tailored interventions to help low-income Mexican American mothers make changes in their diet and physical activity to reduce risk of weight gain. A new pilot study aimed at reducing risk of diabetes in overweight mothers will pilot test a program to improve dietary intake, physical activity, stress responses, and body weight of young low-income overweight mothers.

Obesity Interventions

Researchers continue to identify and test successful strategies to induce and maintain weight loss. Encouraging results emerged from a recent clinical trial in obese but otherwise healthy adults comparing the benefits of weight loss medication, a lifestyle modification program (diet, exercise, and behavioral therapy), or a combination therapy approach. This one-year study found that lifestyle modification plus the weight loss medication, sibutramine, was more than twice as effective as sibutramine alone in inducing weight-loss in study participants. These results contribute important new information for weight-loss intervention. However, because many obese patients also have other conditions that can adversely affect their health, physicians should carefully monitor patients enrolled in weight-loss programs that include weight-loss medications. Another recent advance addressed the difficulty of maintaining weight loss once it is attained. The Study to Prevent Regain ("STOP Regain") study

assigned adult volunteers who had recently managed to lose about 10 percent of their body weight to one of three groups—a face-to-face intervention group; a group that received a similar intervention delivered over the Internet; and a control group that received quarterly newsletter. Both interventions emphasized self-regulation of body weight and daily self-weighing. As compared to the control group, both the Internet and the face-to-face interventions reduced the risk of regaining five pounds or more, but the face-to-face intervention was particularly beneficial in decreasing the amount of weight regained. Furthermore, those who weighed themselves daily also had better weight maintenance. More than 80 percent of study participants were women, making these results particularly encouraging for women. Ongoing clinical intervention trials include the Look AHEAD clinical trial, which was described previously. This trial will examine the health effects of an intervention to achieve and maintain long-term weight loss through physical activity and decreased caloric intake in 5,145 obese adults with type 2 diabetes. 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. Both Look AHEAD and PRIDE are co-supported by the ORWH. Finally, the ongoing Longitudinal Assessment of Bariatric Surgery (LABS) consortium is conducting research on the effects of bariatric surgery (a form of weight loss surgery) on the health and well-being of patients with extreme obesity to identify patients most likely to benefit.

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. Research in this area will be strengthened by new mechanistic studies of the effects of the intrauterine environment (specifically, the effects of maternal obesity or diabetes) on the development of obesity and other metabolic dysfunction in offspring. In parallel, new clinical studies will explore this "fetal origins hypothesis" among children and mothers from diverse racial and ethnic groups. Obesity is commonly associated with insulin resistance, which is a precursor to type 2 diabetes. Recent advances in understanding metabolic factors affecting development of insulin resistance have revealed a new key factor, a fat-cell hormone called RBP4. Studies in animal models and humans indicate that elevated levels of RBP4 directly correlate with obesity and insulin resistance. Moreover, in studies with mice fed a high-fat diet, blocking RBP4 activity appeared to improve insulin resistance, despite weight gain. Thus, RBP4 is a promising new potential therapeutic target for ameliorating insulin resistance to help prevent type 2 diabetes. Finally, a newly funded study in humans will investigate sex differences in the endocrine regulation of fuel metabolism (i.e., differences between women and men in basic pathways regulating storage and metabolism of fats and other energy yielding substrates). A better understanding of sex differences underlying the biology of obesity and other metabolic disorders could have important implications for etiology and treatment of obesity in women and men.

Kidney Disease and End-stage Renal Disease

As of 2004, there were 472,000 people receiving dialysis or living with a kidney transplant because of end-stage renal disease (ESRD). Approximately 10 to 20 million people in the U.S. have earlier stage kidney disease. Diabetes and high blood pressure are the leading causes of kidney failure, and CVD is a leading cause of death for ESRD patients. Prevalence of irreversible kidney failure is much higher in ethnic and racial minorities within the U.S., 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. Encouragingly, a recent analysis by the U.S. Renal Data System shows that kidney failure rates are leveling; however, this was not true for all ethnic and racial groups examined, and troubling racial disparities still remain. # A major 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 ethnic and racial populations at risk. Among its many efforts, the NKDEP recently launched a new Spanish-language initiative to raise awareness about risk factors for chronic kidney disease among Hispanic Americans. The NKDEP has also been promoting an African American Family Reunion Initiative, the goal of which is to encourage African American families to discuss the connection among diabetes, high blood pressure, and kidney disease at reunions and other family gatherings. (See section below on Minority Health Disparities for further information.)

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.

Risk Factors for Kidney Disease and Cardiovascular Disease

ESRD patients are known to have very high rates of CVD. Investigators are still fleshing out the relationship between less serious chronic kidney disease and CVD. A recent study in elderly women and men with a high prevalence of chronic kidney disease found that traditional risk factors for CVD (such as high blood pressure, obesity, and smoking) were associated with the largest increases in CVD death in this population versus novel risk factors for CVD, such as inflammation. The study suggests that interventions that target the traditional risk factors may have the greatest potential to reduce CVD mortality in this population. Additional aspects of this relationship should be revealed by the Chronic Renal Insufficiency Cohort study, an ongoing multicenter, longitudinal cohort study seeking to identify the factors that contribute to the decline in kidney function and the development of CVD in people with chronic kidney disease. Hypertension contributes to both kidney disease and CVD, and a risk factor study utilizing the Nurses' Health Studies I and II has found that habitual coffee consumption was not associated with increased risk of hypertension among participants. Interestingly, however, consumption of caffeinated cola drinks, whether sugared or diet, was associated with an increased risk of hypertension among women in the study population, an association that will bear further study.

Sex/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. It has been proposed that estrogen normally confers protection against renal and cardiovascular complications in many diseases, and that this protection is lost in diabetes. One newly funded research group is investigating whether the mechanism for the apparent protective effect is cross-talk between estrogen and the renin-angiotensin-system—specifically via estrogen inhibition of the angiotensin II/angiotensin-type-1-receptor (AT1R) pathway, which is an important mediator of diabetic kidney complications. In a recent report, the group examined correlations between estrogen, estrogen receptors, and activity of kidney AT1Rs in female and male rats. In biochemical experiments to detect angiotensin II bound to AT1Rs in kidney extracts, they found that female rats normally had less binding activity than males. However, if the female rats had lost estrogen through removal of their ovaries, there was an increase in kidney AT1R binding to the level seen in male rats. There was also a decrease in kidney estrogen receptors. Both of these effects could be overcome through estrogen adminis-

tration. These results extend previous findings and support the hypothesis that estrogen exerts a renal-protective effect by dampening AT1R activity in the kidney. A better understanding of the sex-related differences in kidney function in health and disease may help pave the way to future specific therapies.

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 painful bladder syndrome/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 NIDDK is also supporting the Urologic Diseases in America project. This important project is closing many of the former gaps in knowledge about the prevalence, incidence, treatment, and economic impact of urologic diseases in the U.S. A new Women's Urologic Health Outreach Program is under development. This effort, conducted in partnership with the ORWH and with input from ICs across the NIH, will help to identify and foster critical research and enhance outreach on urologic conditions that predominantly affect women.

Recurrent Urinary Tract Infections

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 nearly seven million doctor visits by women in 2000, and many women suffer from frequent infections. Ongoing research in this area is helping to elucidate the cause(s) and illuminate potential treatment approaches for recurrent UTIs. In one recent advance, researchers at a Specialized Center of Research, co-supported by the ORWH and the NIDDK, identified a mechanism by which uropathogenic E. coli can persist in the urinary tract to cause infection. In mouse models, these bacteria could form quiescent intracellular reservoirs in cells lining the bladder. If bacteria were in a superficial cell layer, treatment of infected bladders with a particular chemical (protamine sulfate) eradicated infection via exfoliation of the infected cells; however, if the bacteria had been introduced into a deeper cell layer, this treatment triggered reemergence and a recurrent infection. This study sheds light on a possible mechanism for recurrent UTIs and also points toward a new potential approach to treating UTIs by expelling bacteria from their host cell havens so that they will be vulnerable to antibiotic treatment.

Painful Bladder Syndrome/ Interstitial Cystitis

Interstitial cystitis (IC), also called painful bladder syndrome, is a chronic pelvic pain disorder whose cause is not yet known. PBS/IC causes recurring discomfort or pain in the bladder and the surrounding pelvic region. Although the number of American adults with PBS/IC is not known with certainty, recent estimates range from 700,000 to one million, and they are mostly women (90 percent). NIDDK-supported basic and clinical research studies are focused on elucidating the cause(s) of PBS/IC and on improving treatment and interventions. The IC Clinical Research Network recently initiated a trial to determine whether the oral drug amitriptyline (Elavil®) can reduce symptoms of pain and frequent urination in patients. To test and validate promising candidate biomarkers for PBS/IC, such as anti-proliferative factor (APF), the NIDDK has launched the Translational Initiative on Interstitial Cystitis Biomarker Screening: APF Validation, which is currently in Phase I. Such biomarkers could not only help PBS/IC patients obtain a diagnosis earlier in the course of their disease, but they also could facilitate research studies of PBS/IC by helping researcher gauge how patients are responding to therapeutic approaches. Fundamental questions about potential causes, risk factors, and prevalence of PBS/IC are being addressed through several large studies, including the Rand IC Epidemiology Study, which is co-supported by the ORWH. New advances in

basic research on PBS/IC include a better basic understanding of how inflammatory pathways mediate bladder damage and may play a role in PBS/IC. With support from the ORWH, the NIDDK recently held an international scientific symposium on PBS/IC that will help to foster future research studies on this complex and challenging condition.

Urinary Incontinence

A conservative estimate is that approximately 13 million Americans, most of them women, suffer from urinary incontinence. Urinary incontinence 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. Two trials are now near completion: (1) a randomized, controlled clinical trial comparing two surgical treatments for stress and mixed incontinence in women; and (2) a trial focusing on treating women with pure or predominantly urge incontinence. The UITN is currently recruiting patients for a third trial, TOMUS (Trial of Mid-Urethral Slings). This trial compares the outcomes of two minimally invasive surgical procedures, which are FDA-approved, to treat stress urinary incontinence in women. The procedures insert a mesh sling or hammock to support the bladder neck so that urine does not leak under stress (such as coughing, laughing, sneezing, or lifting heavy objects). One procedure inserts a retropubic mid-urethral sling and the other a transobturator mid-urethral sling. Both procedures have been shown to be safe and successful in treating stress urinary incontinence, but it is unknown whether one is better than the other. 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 PRIDE clinical study is underway with ORWH support to evaluate the impact of weight loss resulting from a behavioral program on urinary incontinence in overweight and obese women. A newly funded study will conduct an economic analysis of the PRIDE intervention. A recent study utilizing data from the 2001-2002 National Health and Nutrition Examination Survey reported that women with type 2 diabetes or one type of prediabetes (impaired fasting glucose levels) have twice the prevalence of self-reported urinary incontinence as women with normal fasting glucose levels. Encouragingly, positive results on weight loss and urinary incontinence have emerged from a study in participants in the DPP. The study showed that overweight women with prediabetes who lost a modest amount of weight through dietary changes and increased physical activity had a reduced occurrence of urinary incontinence. The results suggest that, for women with prediabetes, choosing a lifestyle intervention to prevent or delay type 2 diabetes could have the added benefit of preventing episodes of urinary incontinence. Finally, the NIDDK is supporting mechanistic studies of how diabetes—both type 1 and type 2—contributes to urinary incontinence in women; the ORWH is helping to foster these studies.

Initiatives

Request for Applications (RFAs)

- **RFA-Announcement of a Limited Competition for the Continuation of the Urinary Incontinence Treatment Network (UITN) (U01)**
  This RFA announced a limited competition to solicit grant applications from investigators whose institutions are currently serving either as a Clinical Center or the Data Coordinating Center for the Urinary Incontinence Treatment Network (UITN) to continue recruitment, intervention, and followup of study participants enrolled in the Trial of Mid-Urethral Slings (TOMUS) and maintain long-term followup of women who completed the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) and the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) clinical trials. (RFA-DK-06-501)

- **Diabetes Research Centers (P30, P60)**
  This initiative solicited new and competing continuation applications for Diabetes Endocrinology Research Centers (DERCs) and Diabetes Research and Training Centers (DRTCs). Both types of centers are designed to support and enhance the national research effort in diabetes and related endocrine and metabolic diseases. (RFA-DK-06-014)
- **Clinical Nutrition Research Unit Core Centers (P30)**
  This RFA invited applications for Clinical Nutrition Research Unit (CNRU) core centers. The CNRUs are core centers that are part of an integrated program of nutrition and obesity-research support provided by the NIDDK. (RFA-DK-06-013)
- **George M. O'Brien Kidney Research Core Centers (P30)**
  This RFA invited applications for George M. O'Brien Kidney Research Core Centers to support both basic and clinical research on kidney disease. Core Centers provide shared institutional and national resources to facilitate basic and clinical research on kidney disease and improve the effectiveness of translating insights from basic biology to clinical practice. The Centers also support pilot and feasibility studies to develop and test innovative approaches to therapy. (RFA-DK-06-010)
- **Silvio O. Conte Digestive Diseases Research Core Centers (P30)**
  This RFA invited applications for Silvio O. Conte Digestive Diseases Research Core Centers (DDRCCs). The DDRCCs are part of an integrated program of digestive and liver diseases research support provided by the NIDDK. (RFA-DK-06-007)
- **Biomarker Development for Diabetic Complications (R21)**
  This RFA solicited applications for exploratory and developmental research on biomarkers for the micro- and macrovascular complications of diabetes. RFA co-sponsors include the NIDDK, NHLBI, and NEI. (RFA-DK-06-004)
- **Toward Imaging the Pancreatic Beta Cell in People (R01)**
  This RFA solicited new and competing continuation applications focused on in vivo detection of beta cell mass, function, inflammation or transplanted islet engraftment, especially using imaging technologies, to facilitate progress in imaging the pancreatic beta cell. It also sought applications to foster development of novel imaging technologies that will provide new opportunities for evaluating and quantifying beta cell mass and function. (RFA-DK-06-003)
- **Specialized Centers Of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50)**
  NIDDK co-sponsored this ORWH initiative to solicit applications for SCOR centers, the purpose of which are to provide opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. (RFA-OD-06-003)
- **The Obese and Diabetic Intrauterine Environment: Long-term Metabolic or Cardiovascular Consequences in the Offspring**
  The purpose of this RFA was to solicit applications investigating the effect of maternal obesity and diabetes on mechanisms that could potentially contribute to obesity, cancer, cardiovascular or metabolic disease in the offspring. RFA co-sponsors include the NIDDK, NHLBI, and NCI. (RFA-DK-05-014)
- **Obesity/Nutrition Research Centers**
  This initiative invited applications for Obesity/Nutrition Research Center (ONRC) grants. The ONRCs are core centers (P30) that are part of an integrated program of nutrition and obesity-research support provided by the NIDDK. (RFA-DK-04-021)
- **Pelvic Floor Disorders Network**
  This NICHD-led RFA invited applications from investigators willing to participate under a cooperative agreement in an ongoing multicenter clinical program designed to investigate problems in women with pelvic floor disorders, including pelvic organ prolapse, urinary incontinence, fecal incontinence, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tracts. RFA co-sponsors included the NICHD, NIDDK, and ORWH. (RFA-HD-05-019)

- **Clinical Nutrition Research Unit Core Centers**
  This initiative invited applications for Clinical Nutrition Research Unit (CNRU) core centers. The CNRUs are core centers (P30) that are part of an integrated program of nutrition and obesity-research support provided by the NIDDK. (RFA-DK-04-020)

Program Announcements (PAs)

- **Translational Research for the Prevention and Control of Diabetes and Obesity (R18)**
  This PA seeks projects to develop cost-effective and sustainable interventions that can be adopted in real world settings for the prevention and control of diabetes and obesity. It specifically seeks research projects based on interventions already proven efficacious in clinical trials to prevent and reverse obesity and type 2 diabetes, to improve care of type 1 and type 2 diabetes, and to prevent or delay its complications. PA co-sponsors include the NIDDK, NINR, and OBSSR. (PAR-06-532)
- **Planning Grants for Translational Research for the Prevention and Control of Diabetes and Obesity (R34)**
  This PA utilizes the R34 mechanism to focus on planning grants for the same research goals as PAR-06-532. PA co-sponsors include the NIDDK and OBSSR. (PAR-06-358)
- **Endoscopic Clinical Research in Pancreatic and Biliary Diseases (R03)**
  Acute and chronic pancreatic and biliary diseases, including gallstones, cancers, and many others, are common in the U.S. and account for considerable morbidity, mortality and health care costs. This PA encourages innovative clinical and epidemiological research into the role of endoscopic retrograde cholangiopancreatography (ERCP) and other endoscopic and imaging techniques in clinical practice. PAR co-sponsors include the NIDDK and NCI. (PAR-06-171)
- **Improving Diet and Physical Activity Assessment (R01)**
  Diet and physical activity are assessed for both surveillance and epidemiologic/clinical research purposes important to prevention and/or understanding of heart disease, cancer, overweight/obesity, and other chronic conditions. The goal of this PA is to promote innovative research (e.g., improved methods for instrument evaluation or assessment tools for culturally diverse populations) to enhance the quality of measurements of dietary intake and physical activity. PA co-sponsors include the NIDDK, NCI, NHLBI, NIA, NICHD, NIMH, NINR, and ODS. (PAR-06-104)
- **Improving Diet and Physical Activity Assessment (R21)**
  This PA encourages exploratory/developmental research grants on the same scientific goals specified in PAR-06-104 above. PA co-sponsors include the NIDDK, NCI, NHLBI, NIA, NICHD, NIMH, NINR, and ODS. (PAR-06-104)
- **Pilot and Feasibility Clinical Research Grants in Kidney or Urologic Diseases (R21)**
  This PA encourages applications for pilot and feasibility clinical and translational research studies and epidemiological studies related to kidney or urologic disease research that address important clinical and translational questions and are potentially of high impact. It is anticipated that such studies may lead to full-scale clinical studies, including diagnostic strategies, epidemiologic studies, or trials in the diagnosis, prevention, pre-emption, or treatment of kidney or urologic disease. (PAR-06-113)
- **Ancillary Studies to Major Ongoing NIDDK and NHLBI Clinical Research Studies (R01)**
  This initiative encourages qualified investigators to conduct ancillary studies of selected ongoing major clinical research studies, including clinical trials, epidemiological studies and disease databases. The PA is supported by the NIDDK and NHLBI. (PAR-06-216)
- **Pilot and Feasibility Clinical Research Studies in Digestive Diseases and Nutrition (R21)**
  The goal of this initiative is to encourage pilot and feasibility clinical and epidemiological research studies of new therapies or means of prevention of digestive and liver diseases and nutritional disorders associated with digestive and liver diseases. (PA-06-301)

- **Basic Research in the Bladder and Lower Urinary Tract (R01)**
  This initiative encourages applications for research studies that focus on basic cellular, molecular, genetic, and developmental mechanisms of the normal and abnormal function of the bladder and lower urinary tract. An important goal of this initiative is to attract new and established investigators from a variety of basic science research areas to apply their knowledge, skills, and tools to studies of the bladder and lower urinary tract. The PA is co-sponsored by the NIDDK, NCI, NIA, and ORWH. (PA-06-254)
- **Exploratory/Developmental Clinical Research Grants in Obesity (R21)**
  The goal of this initiative is to encourage exploratory/developmental clinical studies that will accelerate the development of effective interventions for prevention or treatment of overweight or obesity in either adults or children. Exploratory epidemiological research with a goal of informing translational/clinical research will also be supported within this program. PA co-sponsors include the NIDDK, NHLBI, NCI, and ODS. (PA-06-256)
- **Non-invasive Methods for Diagnosis and Progression of Diabetes, Kidney, Urological, Hematological and Digestive Diseases (R01)**
  This PA encourages the application of imaging and other minimally or non-invasive technologies to detect, characterize, diagnose, identify persons with predisposition to, or monitor treatment of diseases within NIDDK's purview. (PA-06-143)
- **Long-term Weight Maintenance: Basic and Clinical Studies (R01)**
  This PA invites research applications investigating basic and clinical aspects of long-term weight maintenance. Collaborations between basic and clinical researchers are particularly encouraged under this solicitation. PA co-sponsors include the NIDDK, NINR, NIA, and ODS. (PA-06-145)
- **Development of Disease Biomarkers (R01)**
  The goal of this initiative is to validate biomarkers for well-defined human diseases of liver, kidney, urological tract, digestive and hematologic systems, and endocrine and metabolic disorders, diabetes and its complications, and obesity. These are diseases and disorders for which there are no or very few biomarkers, or for which standard biomarkers are currently prohibitively invasive or expensive. PA co-sponsors include the NIDDK, NIBIB, NIAAA, and ODS. (PA-06-147)
- **Secondary Analyses in Obesity, Diabetes, Digestive and Kidney Diseases (R21)**
  This PA encourages applications to support the secondary analysis of existing data sets relevant to diabetes and endocrine and metabolic diseases; digestive diseases and nutrition, including obesity and eating disorders; and kidney, urological, and hematological diseases. A major subject of this announcement is the support of research on overweight and obesity. (PA-06-151)
- **Ancillary Studies of Kidney Disease Accessing Information from Clinical Trials, Epidemiological Studies, and Databases (R01)**
  This PA encourages ancillary studies to ongoing or completed clinical trials and epidemiological studies of kidney disease as well as clinical trials and epidemiological studies for other diseases or populations that lend themselves to the study of kidney disease. (PA-06-163)
- **Diet Composition and Energy Balance (R01)**
  This initiative encourages research investigating the role of diet composition in energy balance, including studies in both animals and humans. Both short- and long-term studies are encouraged, ranging from basic studies investigating the impact of micro- or macronutrient composition on appetite, metabolism, and energy expenditure through clinical studies evaluating the efficacy of diets differing in micro- or macronutrient composition, absorption, dietary variety, or energy density for weight loss or weight maintenance. PA co-sponsors include the NIDDK, NCI, NCCAM, NHLBI, NIA, NIAAA, NICHD, NINDS, and ODS. (PA-06-173)
- **Insulin Signaling and Receptor Cross-talk (R01)**
  The purpose of this initiative is to stimulate novel and innovative research into the fundamental mechanism(s) of action

of the insulin receptor in target tissues in the context of other cellular receptors and signaling pathways, and to broaden understanding of how insulin signals act to regulate coordinated responses between and among insulin responsive tissues. Of particular interest is how such signaling interactions may affect the development and/or progression of diabetes and its complications. PA co-sponsors include the NIDDK and NIA. (PA-06-175)

- **Health Disparities in NIDDK Diseases (R01)**
  This initiative encourages research to understand and mitigate issues of health disparities in high priority diseases within its scope, including 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. (PA-06-182)
- **Proteomics: Diabetes, Obesity, and Endocrine, Digestive, Kidney, Urologic, and Hematologic Diseases (R01)**
  This PA encourages projects that advance research to identify and quantify protein expression patterns, post-translational modification of proteins, and protein-protein interactions on cells, tissues, organ systems relevant to diabetes, obesity, endocrine and metabolic diseases, nutritional function and diseases of the alimentary tract, exocrine pancreas, liver, kidney, bladder and prostate and normal biological processes related to the function of these systems. (PA-06-184)
- **Heterogeneity of Fat Depots: Underlying Basis and Association with Morbidity (R01)**
  The goal of this initiative is to increase understanding of the interactions among adipocytes and other cell types present in various fat depots in order to identify biomarkers of changes in cellular physiology and metabolism brought on by the obese state, which are truly associated with the development of co-morbidities, such as diabetes, atherosclerosis, and hypertension. The long-term goal of this initiative is to identify markers of obesity associated with disease risk that could yield new targets for therapeutics to disrupt this link. PA co-sponsors include the NIDDK, NHLBI, and NIA. (PA-06-186)
- **Pilot and Feasibility Program Related to the Kidney (R21)**
  The goal of this initiative is to foster the development of high-risk pilot and feasibility research by newly independent or established investigators and to develop new ideas sufficiently to allow for subsequent submission of R01 applications. This research should focus on problems relevant to the study of both acute and chronic kidney diseases and their complications in both the adult and pediatric populations. PA co-sponsors include the NIDDK, NCI, NHLBI, and NIA. (PA-05-103)

Conferences and Workshops

- **Imaging the Pancreatic Beta Cell**
  The purpose of this workshop, which was convened on April 24-25, 2006, was to explore progress in the field of imaging or otherwise visualizing the pancreatic islet cell mass to assess its functionality in health and disease. The workshop showcased studies aimed at visualizing the pancreatic islet and/or beta cell in vivo to elucidate the natural history of islet destruction underlying diabetes pathogenesis and to monitor survival during disease therapy.
- **Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop**
  The objective of this workshop, which was convened on December 19, 2005, was to evaluate the current state of development of the artificial pancreas and determine what steps need to be taken to achieve a functional and safe "closed-loop system." This approach to diabetes management and treatment to improve glucose control and avoid hypoglycemia is most relevant to type 1diabetes patients, but it may also benefit certain patients with type 2 diabetes (particularly those who become insulin dependent).
- **Translational Research Grantee's and Advisory Meeting**
  The purpose of this meeting, which was convened on November 14-15, 2005, was to discuss design and analytical approaches applicable to translational research, provide

opportunities for information sharing among translational researchers, stimulate new ideas for translational research, foster a sense of community among translation researchers, and provide guidance on potential future directions for NIDDK translational research efforts.

- **The Intrauterine Environment**
  This meeting was convened on September 26-27, 2006 and focused on the long-term consequences of maternal obesity and diabetes on metabolic disease in the offspring. Potential mechanisms mediating these effects were also addressed.
- **Glomerular Disease**
  This workshop for both basic science and clinical investigators focused on recent observations and potential opportunities for improving diagnosis and therapeutic intervention for human glomerular disease. It was convened on January 24-25, 2005.
- **Basic Research in Interstitial Cystitis: First Annual Investigators Meeting**
  This meeting, which was convened on October 20-21, 2004, brought together grantees funded under an RFA supporting basic research on PBS/IC to discuss research progress, needs, and future directions in this field.

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 U.S. 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 disproportionately affected groups. The NIDDK's Office of Minority Health Research Coordination (OMHRC) oversees the Institute's efforts to address health disparities. In addition to developing and overseeing an NIDDK Strategic Plan on Minority Health Disparities, the OHMRC has established and supports the Network of Minority Health Research Investigators (NMRI), a communication network of biomedical research investigators and technical personnel from traditionally underserved communities: African American, Hispanic American, American Indian, Alaskan Native, Native Hawaiian, and other Pacific Islanders. Through the NMRI, the NIDDK elicits recommendations for strategies to enhance the opportunities and implement mechanisms for support of minority investigators in biomedical research. The NMRI is helping the NIDDK to advance scientific knowledge and contribute to the reduction and eventual elimination of racial and ethnic health disparities. The OHMRC also promotes the NIDDK and the NIH research training programs that help promote diversity in the biomedical research community.

Information and Education Efforts to Reduce Health Disparities

Several recent new or enhanced NIDDK-supported informational activities also address minority health disparities. The National Diabetes Education Program (NDEP) runs a national multicultural type 2 diabetes prevention campaign, which is the first in the nation, with tailored materials and messages for high-risk audiences. Small Steps. Big Rewards. Prevent Type 2 Diabetes campaign materials include motivational tip sheets, as well as print and radio public service advertisements. The most recent part of the campaign, It's Never Too Early to Prevent Diabetes, was launched in April 2006. This campaign is tailored to women with a history of gestational diabetes (GDM) and their offspring. Women with a history of GDM have an increased risk of type 2 diabetes, and children of these diabetic pregnancies are also at higher risk of obesity and type 2 diabetes. GDM disproportionately affects women from racial and ethnic minority groups in the U.S. Campaign materials are available in both English and Spanish. To help promote the Small Steps. Big Rewards. Prevent Type 2 Diabetes campaign, the NDEP has assembled a team of people from across the country who are working to prevent diabetes in their own lives and in their communities. More information can be found online at http://ndep.nih.gov/campaigns/SmallSteps/

SmallSteps_index.htm. The NDEP is jointly sponsored by the NIDDK and the CDC 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.

It is estimated that more than 80 percent of adult non-Hispanic black women in the U.S. are overweight or obese, based on body mass index (BMI) measurement. This places 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, Fit and Fabulous as You Mature, Energize Yourself and Your Family, and Walking...A Step in the Right Direction. WIN also offers several of its publications on nutrition, physical activity, and weight control in Spanish-language versions, including publications that are part of its Healthy Eating and Physical Activity across Your Lifespan series. In 2005, WIN initiated an effort to inform consumers of the availability of its Spanish-language publication, Cómo Alimentarse y Mantenerse Activo Durante Toda La Vida: Consejos para la Futura Mamá. This WIN brochure provides information on women's nutritional needs during pregnancy and outlines the benefits of physical activity during this special phase. The initiative targeted 300 local establishments (e.g., convenience stores, hair salons) with a predominantly Spanish-speaking clientele. Each of the selected sites was located in U.S. cities with a high proportion of low-income Latino residents: Los Angeles, New York, Miami, and Washington, DC.

Racial and ethnic minorities suffer a far greater incidence and prevalence of irreversible kidney failure than Caucasians. Rates of 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 U.S. except for African Americans, in whom high blood pressure-induced kidney damage is also a major cause. To help address these issues, the NIDDK runs the National Kidney Disease Education Program (NKDEP). This educational program seeks to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk (i.e., those with diabetes, high blood pressure, CVD, or a family history of kidney disease), and the availability of treatment to prevent or slow kidney failure in people with chronic kidney disease and those at risk. Among its many efforts, the NKDEP recently launched a new Spanish-language initiative to raise awareness about risk factors for chronic kidney disease among Hispanic Americans. The initiative includes a Web site (http://www.nkdep.nih.gov/espanol/) and a brochure that highlight the connection between kidney disease and its primary risk factors—diabetes and hypertension. Both resources offer additional Spanish-language resources on diabetes, hypertension, and kidney disease. The new materials were developed in collaboration with kidney disease experts and dialogue in Spanish with community-based organizations serving the Hispanic community. The NKDEP has also been promoting an African-American Family Reunion Initiative. The goal of the initiative is to encourage African American families to discuss the connection among diabetes, high blood pressure, and kidney disease at reunions and other family gatherings.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Environmental agents are likely to play a role in a number of important disease that predominantly affect females, including breast cancer, osteoporosis, ovarian dysfunction, 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 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.

The NIEHS has several groups focused on women's health. The Laboratory of Reproductive and Developmental Toxicology conducts basic research underlying important toxicological principles in the context of reproductive and developmental health. A major goal of the Hormones and Cancer Group is to understand how steroid hormones regulate growth and contribute to oncogenesis in target organs, such as the uterus and mammary gland. The Chromatin and Gene Expression Group has a strong interest in the epigenetic regulation of the human breast cancer susceptibility gene BRCA1, the IKK promoter and the estrogen regulated cathepsin D, a protease whose overexpression is closely associated with a poor clinical outcome for patients with breast cancer. Dr. Donna Baird is a reproductive epidemiologist at NIEHS. Her research is focused on fertility, early pregnancy, and epidemiology of uterine fibroids. The NIEHS Comparative Pathobiology Group is studying the pathogenesis/carcinogenesis of tumors that affect the reproductive tract of rodents and humans and assessing the role of environmental and endogenous hormonal factors in the growth of these tumors. By understanding the basic mechanisms of disease, therapeutic interventions can be developed that will help spawn alternative, non-invasive treatments for clinical fibroids and other diseases.

Accomplishments

Breast and Other Cancers

Circadian Clock and Cell Cycle Gene Expression in Mammary Glands

The suprachiasmatic nucleus (SCN) regulates the biological clock in mammals. The expression of genes controlling the biological clock is not limited to the SCN but is found in many cells and tissues, including the mammary gland. The mammary gland is unique because most of its development occurs after puberty, and it goes through cycles of cell proliferation, differentiation, and regression coinciding with pregnancy, lactation, and involution. Recent studies have shown that disruptions in the sleep-wake cycle in female shift workers lead to increased risk of breast cancer presumably by altering circulating levels of the pineal gland hormone, melatonin. An NIEHS-supported research team has discovered a differentiation-dependent profile of mammary epithelial cells. In a mouse mammary epithelial cell line, differentiated cells, and cells that have fully matured to their final state, expression of the clock genes, Per1 and Bmal1, was elevated, but in undifferentiated cells, Per2 was elevated. These changes were consistent with those seen in actual mouse mammary tissue. In both the cells in culture and mammary tissue, elevated Per2 expression was associated with expression of c-Myc and Cyclin D1, which are cell cycle control genes commonly activated in a variety of human tumors, including breast cancer. The results of these studies show that circadian clock genes may play a role in mammary gland development and cellular differentiation. The patterns of gene expression also suggest that interactions between these genes and cell cycle control genes may have implications for not only mammary gland development but also the development of breast cancer.

Polymorphisms in Nucleotide Excision Repair Genes Modify Breast Cancer Risk in Smokers

Breast cancer occurs at different rates in different racial groups. NIEHS-supported researchers determined that African American women smokers with specific combinations of polymorphisms in nucleotide excision repair genes are more susceptible to breast cancer than white women who smoke. Nucleotide excision repair is the primary means by which smoking-induced DNA damage is repaired. There are several known polymorphisms in genes involved in nucleotide excision repair. These investigators conducted a genetic epidemiologic study aimed at determining whether genetic polymorphisms alter the association between smoking and breast cancer. They found that, in general, smoking was a stronger risk factor for breast cancer in African American women than white women. The risks increased even more for African American women with particular patterns of polymorphisms when combined

with different smoking characteristics, such as amount of smoking, duration, and age at smoking initiation. The investigators claim that this is the first study to examine nucleotide excision repair polymorphisms as susceptibility factors for breast cancer in combination with smoking.

Genes Regulated by Estrogen Predict Survival in Hormone-positive Breast Cancers

Breast cancers are classified as hormone receptor positive or negative, depending on whether cell surfaces contain significant levels of estrogen or progesterone receptors. This is a necessary step in determining whether women with breast cancer should be given anti-estrogen therapies, such as aromatase inhibitors or tamoxifen. Aromatase inhibitors are considered the standard of care for postmenopausal women with hormone receptor-positive breast cancer; tamoxifen remains the hormonal treatment of choice for premenopausal women. The prognosis of patients with hormone receptor-positive breast cancer can be highly variable, but the causes of this variably are largely unknown. Recent research has shown that estrogen receptor-positive tumors may be divided into at least three subtypes with different patient outcomes. NIEHS-supported researchers first identified estrogen-regulated genes by treating an estrogen receptor-positive breast cancer cell line with estradiol and performing microarray analysis. They applied this gene-set to 65 primary breast cancer tumors. Further analyses refined the gene set to 822 genes that optimally defined two groups based on the genes activated in the tumors. The poor-prognosis group showed high expression of cell proliferation and anti-apoptosis genes, while the good-prognosis group showed high expression of estrogen and GATA3-regulated genes. This study shows that this set of estrogen-regulated genes may be useful in predicting the survival outcome and recurrence of cancer in hormone-receptor positive breast cancer patients treated with tamoxifen.

Genetic Testing Misses Some Breast Cancer Gene Mutations

Women who are at risk for familial breast or ovarian cancer are routinely tested for mutations in BRCA1 and BRCA2. New research by an NIEHS-supported scientist has discovered that current commercial testing fails to detect a significant number of mutations. DNA- and RNA-based tests were conducted to detect genomic rearrangements in BRCA1 and BRCA2 and germ-line mutations in CHEK2, TP53, and PTEN in subjects from more than 300 families in the U.S. with four or more cases of breast or ovarian cancer. Specimens from these cases had been tested with commercially-available assays and found negative for BRCA1 and BRCA2 mutations. In this study, of the 300 subjects, 17 percent were found to have previously undetected mutations. Thirty-five had rearrangements of BRCA1 and BRCA2, 14 had CHEK2 mutations, and three had TP53 mutations. This study demonstrates that commercial genetic testing does not detect all mutations in women with a strong familial history of breast and ovarian cancer. These findings are important because risk reduction interventions for those with mutations are highly effective. Commercial testing should be expanded to include these and possibly other mutations so that at-risk women have the best information available when deciding to undergo invasive interventions, such as preventive mastectomy or ovary removal.

Pro-inflammatory Lymphocytes Promote Breast and Intestinal Cancer

Breast cancer is the most common form of cancer in women and strikes one out of every eight women. There have been numerous research studies showing that the risk of both these cancers is reduced in women who regularly take non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen. These findings suggest that inflammation contributes to the development of intestinal and breast carcinogenesis in humans. There are no good experimental animal models to investigate the link between inflammation and breast cancer. A recent study by an NIEHS-supported research team has made progress in the ability to test the inflammation/cancer link. These researchers injected mice genetically prone to develop cancerous intestinal polyps and breast tumors with a specific subtype of pro-inflammatory T cells, which induced inflammatory bowel disease. The injected mice developed many more intestinal polyps than did the non-inject-

ed controls. Seventy percent of the female mice that received the pro-inflammatory T cells also rapidly developed mammary tumors. There was no evidence of mammary tumor development in the untreated female mice. Neither the intestinal polyps nor the mammary tumors developed in mice that received both pro- and anti-inflammatory T cells. Down regulation of the enzyme, cyclooxygenase-2 (COX-2), a known target of non-steroidal anti-inflammatory drugs, was observed coincident with tumor regression. These studies define a new model for inflammation-driven mammary tumor development and represent an important new tool to investigate the inflammation/cancer link. The findings also allude to the broader applicability of anti-inflammatory therapies in the treatment of specific types of cancer that are responsive to COX-2 inhibitors and other non-steroidal anti-inflammatory drugs.

A Mitochondrial DNA Polymorphism Is Associated with Invasive Breast Cancer in African American Women

Mitochondria generate oxygen-derived free radicals during normal metabolism. Free radicals damage both mitochondrial and nuclear DNA and, in turn, promote the development of cancer. A mitochondrial DNA polymorphism known as G10398A, which alters an important site of free radical production, has been associated with several neurodegenerative disorders. In a preliminary study in African American women, NIEHS-supported investigators found an association between the 10398A allele and invasive breast cancer in African American women. Women with the G10398A allele had almost three times the risk of having invasive breast cancer as those without it. A larger study was conducted in both African American and white women. African American women with the 10398A allele had a significantly increased risk of invasive breast cancer. No association was detectable in the population of white women. This study provides new evidence that mitochondrial genome differences may contribute to breast cancer susceptibility and may play a role in the differences in incidence of breast cancer between African American and white women. The magnitude of the difference in risk suggests that this polymorphism is an important, newly discovered risk factor to consider in the etiology of breast cancer in African American women.

Repair of DNA Damage Differs between Sisters with and without Breast Cancer

Breast cancer results from complex interactions of genes and environmental exposures. Individuals differ in both their unique genetic makeup and the exposures that they encounter throughout their lifetimes. Damage to DNA is known to be a critical early step in the development of cancer since unrepaired damage leads to alterations in cellular functions. Therefore, individual differences in DNA repair capacity may influence the risk of developing cancer. NIEHS-supported researchers evaluated the DNA repair capacity in breast cancer patients by analyzing sister pairs, one with breast cancer and one without. Cell culture lines for breast cancer patients and control sisters were obtained from the Metropolitan New York Registry of Breast Cancer Families. The cell cultures were treated with a DNA-damaging agent followed by a standard DNA repair assay, known as nucleotide excision repair, to determine the extent of the damage and repair capacity. DNA repair capacity of breast cancer patients was statistically lower than that of their sisters without breast cancer. This difference translated into a two-fold increase in the risk for developing breast cancer. Additional data analyses resulted in a dose-dependent association between deficient DNA repair capacity and breast cancer risk. The finding may become a valuable marker to identify women who are at high risk for the disease, especially among families with high incidence of breast cancer.

Mice Expressing a Mammary Gland Specific R270H Mutation in the p53 Tumor Suppressor Gene Mimic Human Breast Cancer Development

The tumor suppressor gene p53 has an apparent role in breast tumor development in humans, as approximately 30 percent of sporadic tumors acquire p53 mutations. Li-Fraumeni syndrome patients carrying p53 mutations frequently develop breast tumors at early age. Conditional expression of a targeted mutation is used to analyze the role of the human R273H tumor-associated hot-spot mutation in p53 in mammary gland tumorigenesis. p53.R270H mutant mice (i.e., mice

with mammary gland-specific expression of the p53.R270H mutation, which is equivalent to human R273H at physiologic levels) develop mammary tumors at high frequency, indicating that the R270H mutation predisposes for mammary gland tumor development and acts in a dominant-negative manner in early stages of tumorigenesis. Spontaneous tumor development in these mice is further accelerated by 7,12-dimethylbenz(a)anthr acene (DMBA) treatment at young age. The majority of spontaneous and DMBA-induced neoplasms from the p53.R270H mutant mice are estrogen receptor alpha positive, and expression profiles of genes implicated in human breast cancer appear similarly altered. Conditional knock-in mouse models (as the p53.R270H mutant), with mutations equivalent to those found in humans targeted into the mouse genome, show tumor responses and tumor types highly comparable to human cancer. As such, these models are very suitable to establish precise genotype-phenotype relationships between p53 hot-spot mutations found in humans and tumorigenesis in specific tissues, like the breast. Ultimately, these mouse models, which are highly relevant to human disease, can be used to study the effectiveness of novel cancer therapies.

Tamoxifen and Estrogen Induce Chromosome Breaks in DNA Repair-deficient Cells

Tamoxifen, an anti-estrogen used in 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 project are to establish a mechanism for the genotoxicities of tamoxifen and estrogen and to find a safer alternative to tamoxifen. Oligodeoxynucleotides containing a single defined DNA adduct will be prepared by automated DNA synthesis. Using these site-specific modified oligodeoxynucleotides, the mutagenic and repair potential of estrogen and anti-estrogen 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 investigators 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.

Secretome Analysis of Microarray Data Reveals Extracellular Events Associated with Proliferative Potential in a Cell Line Model of Breast Disease

It is widely believed that breast cancer develops in a multistep process, with premalignant lesions preceding invasive carcinoma. The characterization of molecular events associated with premalignant progression would improve the understanding of carcinogenesis and greatly benefit the development of early detection methods and chemoprevention strategies. However, the molecular biology of precancerous breast disease is poorly understood. To better characterize extracellular events associated with disease progression, NIEHS-supported researchers analyzed gene expression profiles for the set of genes coding for secreted proteins (the secretome) in a cell line model of human proliferative breast disease (PBD). PBD describes a series of preneoplastic changes in the inner lining of milk glands associated with a dramatic increase in the risk of breast cancer. A series of cell lines with increasing proliferative propensity and cell cultures were grown on matrigel to emulate in vivo growth; extracellular matrix interactions were used. Microarray analysis identified two clusters of secretome genes with expression profiles correlating to PBD progression. Reverse transcription-poly-

merase chain reaction validation demonstrates the reliability of the microarray results. Some of the identified genes have previously been associated with breast malignancies, and these results suggest that changes in expression for these genes begin in the premalignant stage, offering potential use for early detection and as chemotherapeutic targets.

Drug-induced NAG-1 Inhibits Tumor Growth

Researchers from the NIEHS, the NCI, the U.S. EPA, the University of Tennessee-Knoxville, and the University of Occupational and Environmental Health in Kitakyushu, Japan studied the interaction of a potential anticancer drug and a gene with anti-tumor properties. The team confirmed that nonsteroidal anti-inflammatory drug-activated gene (NAG-1) suppresses tumor growth in mice and that the expression of NAG-1 can be controlled with anticancer drugs. These findings are important in the fight against cancer because drugs that target NAG-1 may lead to the development of new cancer treatments. Since most of the information about NAG-1 is based on in vitro experiments, the team wanted to confirm that the up-regulation of NAG-1 is associated with inhibition of tumor development in vivo. They injected MCF-7 (breast cancer cell line) cells into controls and treated nude mice by injecting 5F203. (5F203 is the active moiety of an anticancer drug that is in the early Phase I clinical studies in cancer patients.) The investigators then measured the size of the mammary tumors produced and used polymerase chain reaction to measure NAG-1 levels in the tumors. The median tumor weight in treated mice decreased by up to 75 percent. Needle biopsies of the tumors taken six and 24 hours after 5F203 injection indicated a dose-dependent increase of NAG-1 expression compared with controls. Taking all of the data into account, treating mice with 5F203 increased NAG-1 expression and inhibited tumor growth in vivo. This outcome indicates that NAG-1 is an important mediator for the activity of 5F203 and provides a possible treatment for cancer.

The Sister Study: Environmental and Genetic Risk Factors for Breast Cancer

The Sister Study is a unique study exploring gene-environment interactions in breast cancer development. It has begun nationwide recruitment. More than 27,000 women have enrolled in the study to date. Recruitment is ongoing with emphasis on hard-to-reach populations and communities. The study will look at how genes, activities of daily life, and environmental exposures affect breast cancer risk. To get the information quickly, this study recruits 50,000 symptom-free women who have a sister that had breast cancer. These women are at increased risk of breast cancer, share many genes with their affected sibling, and would have experienced many of the same exposures. For these reasons, it is expected that a sufficient number of women will develop breast cancer within 10 years, and their genes and exposures can be compared with those women in the study who did not develop the cancer. Approximately 150 new cases of breast cancer have been reported to date. A broad range of exposures will be examined, including personal care and household products, workplace exposures, and dietary factors. A number of advocacy groups are working with the NIEHS on this project, including the American Cancer Society, Sisters Network, Inc., the Susan G. Komen Breast Cancer Foundation, and the Y-ME Breast Cancer Organization.

Overexpression of a Mitochondrial DNA Repair Enzyme Protects Normal Cells from Cancer Drugs

Current cancer treatments include drugs known as alkylating agents. They work by chemically modifying DNA, which disrupts normal DNA replication and results in cell death. These effects are especially toxic to the rapidly growing and dividing cancer cells to which the drugs are targeted; however, normal cells are inevitably affected as well. Proteins known as DNA repair enzymes are present in cells to target damaged DNA and reverse the modifications caused by alkylating agents. One such enzyme is methylguanine methyltransferase (MGMT). MGMT directly reverses the chemical modification guanine, one of the four building blocks of DNA, allowing normal replication to take place. Properly targeted DNA repair enzymes could be used to combat

drug toxicity in normal cells and alleviate side effects. However, DNA is present both in the nucleus of a cell as well as in mitochondria, and it is currently unknown whether damage to nuclear or mitochondrial DNA plays a larger role in cell toxicity. NIEHS-supported scientists studied whether or not MGMT could reverse the toxic effects of alkylating agents. They did this by causing an overexpression of MGMT in cultured human cells and targeted the enzyme either to nuclei or mitochondria. The cells were then exposed to DNA alkylating agents commonly used in chemotherapy. Investigators found that cells overexpressing MGMT had better survival rates than cells expressing low levels of MGMT and that MGMT targeted to the mitochondria was as effective as or better than nuclear-targeted MGMT in preventing cell killing, depending on the cell type and chemical agent used. These results suggest a potential strategy for reducing the harmful side effects of chemotherapy by making healthy cells more resistant to alkylating drugs. They imply that it may be possible to engineer such cells and introduce them into patients before beginning chemotherapeutic regimens. They also suggest that DNA repair enzymes, such as MGMT, are promising focuses of such strategies and that mitochondria, as well as nuclei, are equally important targets of these enzymes.

Bone Research

Mutation Causes Some Cases of Brittle Bone Disease

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a group of genetic bone disorders resulting in frequent fractures. It is caused by structural changes in collagen proteins. A newly identified gene mutation helps explain a subset of cases of OI whose origin had been mysterious. This mutation is responsible for up to 15 percent of OI cases. The mutation prevents collagen proteins from being properly modified after they are produced. Cartilage-associated protein (CRTAP) interacts with the enzyme responsible for the hydroxylation of the collagen protein. The mutation in CRTAP prevents this interaction and thus prevents the protein modification, resulting in damaged collagen and poor bone formation. Results indicate that a partial loss of CRTAP function caused OI and that a complete loss caused an even more severe form of the disease. These findings could have important diagnostic implications, especially surrounding suspected child abuse cases. Until now, the only known genetic cause of OI was a structural mutation in type I collagen. This finding adds a new dimension in terms of DNA testing. It also may also offer clues to the causes of connective tissue diseases that affect other parts of the body and gives insight into the basic mechanism of collagen formation.

CRTAP Mutations Are Associated with the Clinical Spectrum of Recessive Osteogenesis Imperfecta

Prolyl hydroxylation is a critical post-translational modification that affects structure, function, and turnover of target proteins. Prolyl 3-hydroxylation occurs at only one position in the triple-helical domain of fibrillar collagen chains, and its biological significance is unknown. CRTAP shares homology with a family of putative prolyl 3-hydroxylases (P3Hs), but it does not contain their common dioxygenase domain. Loss of CRTAP in mice causes an osteochondrodysplasia, which is characterized by severe osteoporosis and decreased osteoid production. CRTAP can form a complex with P3H1 and cyclophilin B (CYPB), and Crtap-/- bone and cartilage collagens show decreased prolyl 3-hydroxylation. Moreover, mutant collagen shows evidence of over modification, and collagen fibrils in mutant skin have increased diameter consistent with altered fibrillogenesis. In humans, CRTAP mutations are associated with the clinical spectrum of recessive osteogenesis imperfecta, including the type II and VII forms. Hence, dysregulation of prolyl 3-hydroxylation is a mechanism for connective tissue disease.

Urogenital Research

Urogenital Carcinogenesis in Female Mice Induced by In Utero Arsenic Exposure Is Exacerbated by Postnatal Diethylstilbestrol Treatment

Inorganic arsenic is a human carcinogen, and environmental exposure through contaminated drinking water is a major concern throughout the world. Transplacental inorganic arsenic carcinogenicity, together with postnatal

exposure to diethylstilbestrol or tamoxifen, was studied. Pregnant mice were exposed to arsenic in the drinking water. Female offspring were injected with diethylstilbestrol or tamoxifen. Arsenic induced some urogenital system tumors, including mostly benign tumors of the ovary and uterus, and adrenal adenoma. Diethylstilbestrol induced some tumors (primarily cervical) but when given after in utero arsenic, it greatly enhanced urogenital tumor incidence, multiplicity, and progression. Arsenic plus diethylstilbestrol increased ovarian, uterine, and vaginal tumors, and urinary bladder proliferative lesions, including three transitional cell carcinomas. Tamoxifen alone did not increase urogenital tumors or affect arsenic-induced neoplasia but did increase arsenic-induced uroepithelial proliferative lesions. Uterine and bladder carcinoma induced by arsenic plus diethylstilbestrol greatly overexpressed estrogen receptor-alpha (ER-alpha) and pS2, an estrogen-regulated gene. In neonatal uteri, prenatal arsenic increased ER-alpha expression and enhanced estrogen-related gene expression induced by postnatal diethylstilbestrol. Gestational arsenic exposure is a complete carcinogen in the female mouse that targets the urogenital system, and exposure to the synthetic estrogen, diethylstilbestrol, after arsenic increased tumor incidence, multiplicity, and progression.

Neurologic Research

Genome-wide Screen for Neural Tube Defects Reveals Candidate Genes on Chromosomes 7 and 10

Neural tube defects are the second most common severely disabling form of human birth defects. Neural tube defects are thought to be caused by a complex interaction between a person's genetic makeup and environmental exposures. The most important environmental risk factor for neural tube defect is insufficient folate consumption by the mother around the time of conception. Folate supplementation reduces the risk of neural tube defect recurrence by 50 to 70 percent, but it does not entirely eliminate the risk, suggesting underlying genetic factors. However, studies of folate and other developmentally related genes in humans have failed to identify a definitive gene causing neural tube defects. A nationwide collaborative effort is being conducted in 14 research facilities across the U.S. and is funded by the NICHD, the NINDS, and the NIEHS. New insights have been gained as to the possible sites of a neural tube defect gene or genes. Using families with more than one occurrence of a neural tube defect, researchers have identified two candidate genes on human chromosome seven and three on chromosome 10. The data from this study represent an important step in narrowing the search for the gene or genes responsible for neural tube defects and bringing the medical community closer to the day when individual predictions of neural tube defect risk may be possible.

Depression

Depression and Pesticide Exposures in Female Spouses of Licensed Pesticide Applicators

This nested case-control study evaluated the association between depression and pesticide exposure among women. The study population included female spouses of private pesticide applicators enrolled in the Agricultural Health Study. Cases were women who had physician-diagnosed depression requiring medication. Lifetime pesticide use was categorized as no exposure (never mixed/applied pesticides), low exposure (up to 225 days), high exposure (greater than 225 days), and a history of diagnosed pesticide poisoning. After adjustment for state, age, race, off-farm work, alcohol, cigarette smoking, physician visits, and solvent exposure, depression was significantly associated with a history of pesticide poisoning, but it was not associated with low or high cumulative pesticide exposure. This study highlights the importance of preventing pesticide poisoning because the chronic effects of those poisonings may contribute to high rates of depression.

Autoimmune Diseases

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. The role of genetic susceptibility in lupus has been

extensively examined, but the idea that lupus can be explained solely by genetics is not supported by recent studies. The concordance rate among monozygotic twins is currently thought to be 25 to 33 percent, which is substantially lower than the 75 percent figure derived from small studies subject to substantial selection bias that were published in the 1960s and 1970s. There is a clear need to look beyond genetics to understand this and other autoimmune diseases. Studies by NIEHS researchers represent a broader approach to studying lupus. It is an approach that is based on the often-cited idea that lupus involves a combination of and interaction between genetic and environmental factors. This work focuses on genetic factors and on measures of endogenous hormonal exposures, exogenous sources of estrogen, and on environmental exposures that may affect the risk of lupus and of other autoimmune diseases. Importantly, sound methodologic designs to develop the studies within this research program, including population-based approaches to identifying patients and appropriate comparison groups, have been used. Innovative approaches to exposure assessment within the context of case-control studies have also been developed. The specific studies that have been completed or are currently underway within this project include the following seven studies: (1) The Carolina Lupus Study, the first large, population-based case-control study of genetic, hormonal, and environmental risk factors for lupus in the U.S.; (2) Dietary Risk Factors for Lupus, a prospective analysis using data from the Nurses' Health Study (I and II); (3) Parity and Risk of Systemic Sclerosis, an analysis using a unique resource, the hospitalization and pregnancy registries covering the entire population of Sweden; (4) Pesticide Exposure and Risk of Rheumatoid Arthritis, an analysis using the Agricultural Health Study cohort of spouses of licensed pesticide applicators; (5) Antinuclear Antibodies and Other Markers of Immune Function, an analysis using the controls in the Carolina Lupus Study to determine the prevalence of antinuclear antibodies in the general population and the relationship between specific demographic and environmental exposures with high-titer levels of antinuclear antibodies in the absence of diagnosed disease, also including an analysis of serum DDE levels in relation to immunoglobulin and autoantibodies among African American farmers; (6) The Early Disease Course of Systemic Lupus Erythematosus, an analysis of mortality, quality of life, health care utilization, and employment status in the first 4 years post-diagnosis of lupus; and (7) Silica Exposure and Small Vessel Vasculitis, an analysis of occupational exposures in 129 ANCA-glomerulonephritis patients diagnosed between 1997 and 2003 in North Carolina, South Carolina, Georgia, and southern Virginia, as well as 109 population-based controls.

Cooperative Study Group for Autoimmune Disease Prevention

Autoimmune diseases are debilitating, chronic illnesses that affect multiple organ systems and disproportionately afflict women. Type 1 diabetes afflicts more than 600,000 people in the U.S., with peak onset occurring in childhood. Although insulin treatment is available, long-term complications include kidney failure, blindness, amputations, and accelerated cardiovascular disease. The NIEHS is looking into research in this area. The ultimate goal of this research is to develop the knowledge base necessary to design preventive interventions that could be administered efficiently and safely to at-risk individuals or to the general population, including infants and children.

Maternal and Child Health

Norway Mother and Child Cohort Study (MoBa)

The Norwegian Mother and Child Cohort Study, also called MoBa, is an ongoing, long-term, prospective cohort study of 100,000 pregnant Norwegian women and their children. In collaboration with the Norwegian National Public Health Institute (NIPH), the NIEHS is supporting the collection of additional biologic specimens from the pregnant women. These specimens will be used for the measurement of environmental exposures. A variety of exposure and health variables on babies, mothers, and fathers are collected. Records from the cohort study will also be linked to routine national health registries. MoBa provides a valuable opportunity to assess the role of environmental exposures in the health of women and their children.

Trends in Fetal and Infant Survival Following Preeclampsia

Management of preeclampsia often culminates in induced delivery of preterm infants. Although early termination protects the fetus from an intrauterine death, the newborn faces increased risks associated with preterm delivery. NIEHS researchers assessed the effect of early delivery of preeclamptic pregnancies on rates of fetal and infant survival. Among these pregnancies, inductions before 37 weeks increased from 8 percent in 1967-1978 to nearly 20 percent in 1991-2003. During this period, the adjusted odds ratio (OR) for stillbirth decreased from 4.2 to 1.3 for mothers with preeclampsia compared with mothers without this condition. During the same period, the OR for neonatal death after preeclamptic pregnancy remained relatively stable. Later, infant and childhood mortality also showed little change. Fetal survival in preeclamptic pregnancies has vastly improved over the past 35 years in Norway, presumably because of more aggressive clinical management. However, the relative risk of neonatal death following a preeclamptic pregnancy has not changed.

Menopause and Other Reproductive-related Research

North Carolina Menopause Study

Relatively little is known about the effect of potential toxicants, including organochlorines, such as polychlorinated biphenyls (PCBs) and DDE, the long-lasting breakdown product of the pesticide DDT. One recent study conducted by epidemiologists at the NIEHS and the University of North Carolina, Chapel Hill reported an association between elevated blood levels of DDE and earlier age at menopause, but this was based on a cross-sectional study design. The North Carolina Menopause Study is a prospective study designed to assess timing of menopause in relation to organochlorine exposures, with exposure measurements taken during the reproductive years.

Pesticide Exposure and Timing of Menopause

Age at menopause has implications for fertility and risk of hormonally related chronic diseases. Some pesticides disrupt reproductive hormones or are toxic to the ovary, but little is known about the association between pesticide exposure and timing of menopause. Cox proportional hazards modeling was used to examine the association between use of pesticides and age at menopause among women living and working on farms in Iowa and North Carolina. Premenopausal women between the ages of 35 and 55 years were followed from enrollment to the date of their last menstrual period or their final followup interview if still premenopausal at the end of the study. Approximately 62 percent of the women reported ever mixing or applying pesticides; women who had never used pesticides were the comparison group for all analyses. After controlling for age, smoking status, and past use of oral contraceptives, the median time to menopause increased by approximately three months for women who used pesticides and by approximately five months for women who used hormonally active pesticides. Pesticide use may be associated with a later age at menopause. The results of this study suggest that use of certain pesticides may lead to a later age at menopause.

Menstrual Patterns, Menopause, and Women's Health

Ovarian function encompasses the cyclical production of estrogen and progesterone during the reproductive years and the timing of ovarian failure or menopause. Thus, ovarian function 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 the following: (1) Menstrual Cycle Patterns in Relation to Risk of Chronic Diseases is conducting analyses using prospectively collected menstrual cycle data from more than 800 women who were 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) The Menopausal Status and the Menopausal Transition study conducted analyses using data from national population-based studies (i.e., the National Health and Nutrition Examination Survey III and the National Health Information Survey). This study also included methodologic research that compared different analytic methods for assessing associations with timing of menopause; (3) The Pesticide Exposure, Menstrual Cycle Characteristics and Timing of Menopause study conducted analyses using data from the Collaborative Perinatal Project, the Agricultural Health Study, and a longitudinal study examining biological measures of DDE and PCB exposure in relation to timing of natural menopause. This 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.

Definition of Estrogen Receptor Pathway Critical for Estrogen Positive Feedback to Gonadotropin-releasing Hormone Neurons and Fertility

The mechanisms through which estrogen regulates gonadotropin-releasing hormone (GnRH) neurons to control mammalian ovulation are unknown. NIEHS researchers found that estrogen positive feedback to generate the preovulatory gonadotropin surge was normal in estrogen receptor (ER) beta knockout mutant mice, but it was absent in ER alpha mutant mice. An ER alpha-selective compound was sufficient to generate positive feedback in wild-type mice. As GnRH neurons do not express ER alpha, estrogen positive feedback on GnRH neurons must be indirect in nature. To establish the cell type responsible for this, a neuron-specific ER alpha mutant mouse line was generated. These mice failed to exhibit estrogen positive feedback, demonstrating that neurons expressing ER alpha are critical. The researchers then used a GnRH neuron-specific Pseudorabies virus tracing approach to show that the ER alpha-expressing neurons innervating GnRH neurons are located within rostral periventricular regions of the hypothalamus. These studies clarify the mechanism of estrogen positive feedback to GnRH neurons by providing definitive evidence that it is ER alpha, not ER beta, which is critical. Moreover, the neuron-specific ablation of ER alpha renders mice infertile with a complete ablation of estrogen positive feedback. Thus, estrogen acts indirectly on GnRH neurons to bring about positive feedback driving ovulation, and the ER alpha-expressing neurons mediating this pathway are located in periventricular regions.

Endometrial Cancer

Endometrial cancer is the most frequently diagnosed gynecologic malignancy in the U.S., but it 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, which is described previously.

Menstrual and Reproductive Factors in Relation to Risk of Endometrial Cancer

Menstrual, reproductive, and contraceptive factors have been associated with risk of endometrial cancer in populations where the incidence of this tumor is high. To investigate associations among these factors in a low-risk population with a low prevalence of hormone replacement therapy, a cohort study of women employed in the textile industry in Shanghai, China was conducted. Menstrual, reproductive, and other factors were ascertained at baseline in 1989 to 1991, and women were followed for incident endometrial cancer

through December 31, 1998. Cox proportional hazards modeling was used to estimate hazard ratios and 95 percent confidence intervals. Risk of endometrial cancer decreased with increasing age at menarche. Among menopausal women, risk increased with age at menopause and increasing years of menstruation. Compared to women with one live birth, risk was increased in nulliparous women. Risk was decreased with increasing age at first live birth. There was a decreased risk associated with ever use of an intrauterine device and use of oral contraceptives for two or more years. This prospective study confirms findings from previous case-control studies relating menstrual, reproductive, and contraceptive factors and endometrial carcinoma.

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 therapy to treat symptoms of menopause and in oral contraceptives. The report cites data from human epidemiology studies that show an association between menopausal estrogen 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 they may protect against ovarian and endometrial cancers.

Environmental PCB Exposure and Risk of Endometriosis

Hormonally active environmental agents have recently been associated with the development of endometriosis. NIEHS-supported researchers conducted a study to assess the relationship between endometriosis, an estrogen-dependent gynecological disease, and 62 individual polychlorinated biphenyl (PCBs) congeners. The researchers enrolled 84 eligible women between 18 and 40 years old who were undergoing laparoscopy for study. Thirty-two women had visually confirmed endometriosis at laparoscopy, while 52 did not. A significant, nearly four-fold increase in risk of endometriosis was observed for the sum of four PCB congeners reported to have anti-estrogenic properties. The magnitude of this effect decreased to approximately three-fold after adjusting for serum lipids, gravidity, and current cigarette smoking, suggesting possible confounding by these factors. These effects may reflect both the lipophilic nature of PCBs and the hormonal dependency of endometriosis. These findings support a role for dioxin in the etiology of endometriosis in that anti-estrogenic PCB congeners may be a surrogate for dioxin-like activity of these compounds. No association was seen for the estrogenic compounds and risk of endometriosis.

Oxidative Stress and Endometriosis

Little is known about the etiology of endometriosis. However, in the presence of oxidative stress, reactive oxygen species might increase growth and adhesion of endometrial cells in the peritoneal cavity, leading to endometriosis and infertility. Within a study investigating persistent organic compounds and endometriosis, the association between oxidative stress and endometriosis was evaluated. There was a weak association between thiobarbituric acid-reactive substances and endometriosis, after adjusting for age, body mass index, current smoking, hormone use in the past 12 months, gravidity, serum vitamin E, serum estradiol, and total serum lipids. These results suggest that oxidative stress might play a role in the development and progression of endometriosis.

Uterine Fibroid Study

Uterine leiomyomas (fibroids) are the leading indication for hysterectomy in the U.S. Despite the morbidity and high medical costs associated with fibroids, there has been little epidemiologic study of this condition in the U.S. Uterine leiomyomas are histologically identifiable as benign smooth muscle tumors with varying amounts of associated fibrous tissue. Many women have more than one uterine leiomyoma, but each appears to be clonally distinct. Several specific cytogenetic changes have been identified in tumor tissue, but most show no chromosomal abnormalities. These benign tumors are hormone-dependent. They develop after puberty and regress after

menopause. Both estrogen and progesterone are considered important stimulants, or at least permissive factors for tumor growth. To address the research needs in this field, NIEHS investigators have designed three studies. The first is a large epidemiologic study, the NIEHS Uterine Fibroid Study, designed to estimate the age-specific cumulative incidence of leiomyomas in black and white women between the ages of 35 and 49 years. This study will also identify risk factors for the condition, compare growth mediating factors in tumor and matching myometrial tissues collected at time of hysterectomy, and identify factors associated with development of fibroid symptoms, including pelvic pain and uterine bleeding. The second study, the Fibroid Growth Study, is a clinical study of fibroids designed to describe fibroid growth and compare the growth-mediating factors in growing vs. non-growing tumors. The third study, the Postpartum Uterine Regression Study, monitors fibroid change with pregnancy and postpartum uterine regression. After estimating the age-specific incidence of uterine fibroids for black and white women, risk factors for uterine fibroids were examined. Pregnancy is protective, though not those that occur before the mid-twenties. Alcohol appears to increase risk. The location of fibroids is somewhat different for parous and nonparous women, and prenatal exposure to DES is associated with increased development of fibroids. Increasing LH is associated with increased prevalence of the tumors, though LH may not be having direct proliferative effects. There is no evidence for increased risk of fibroids with oral contraceptive use or with variability in menstrual-cycle length. NIEHS researchers found a small increase in risk with increased BMI, which is similar to findings from other studies. The investigators also found that exercise is protective. Smoking was not associated with increased risk. Questionnaires collected information on early-life exposures and several environmental/occupational exposures. While few factors showed associations with fibroid development, an association of childhood use of insect repellent with fibroids was found. Fasting insulin and IGF-I in blood specimens were collected from participants because researchers hypothesized that both would be risk factors for fibroids. Surprisingly, both tended to be protective, and diabetics were actually significantly less likely to have fibroids. For the clinical study of fibroid growth, NIEHS researchers are working to determine accurate volumetric measures of nearly 600 tumors so that they can model growth. Microarrays of tumor vs. normal myometrium have been completed, and the data are being analyzed. The third study, which is monitoring fibroid change during postpartum uterine regression, is still ongoing. Approximately 300 of the target 400 women have been enrolled, and approximately 180 have completed the postpartum ultrasound.

Other Related Research

Health Effects of Exposures in Agriculture Communities: The Agricultural Health Study

The Agricultural Health Study is a collaborative effort among the NIEHS, the NCI, and the EPA. Farmers appear to be at increased risk for several specific cancers, and these cancers tend to be ones that are increasing in incidence throughout the world. Although many studies have been done, much of this work has been retrospective or has been based on limited information related to exposures. In addition, while there is some evidence for non-cancer health effects associated with many of these same exposures, much less work has been done. The NIEHS collaborative study of non-cancer health effects among licensed pesticide applicators and their families represents one of the largest cohorts of farmers studied to date. The NIEHS is among the first to explore health effects among spouses and children who have substantial direct and indirect exposure to pesticides. Recent results from the Agricultural Health Study include: long-term exposure to pesticides is associated with increased reporting of neurological symptoms typically seen following acute exposures; there is increased risk for accident mortality among farm children; there is decreased fertility associated with parental use of solvents and obesity in men; there is a consistent and strong association between organophosphate pesticides as well as the herbicide, chlorimuron-ethyl, and wheeze among commercial pesticide applicators; there is a link between pesticide use and self-reported Parkinson's disease; there is an absence of an association between pesticides and farm factors and risk for rheumatoid arthri-

tis; there is a link between specific hormonally active pesticides and late age at menopause; and there is a link between personal use of agricultural pesticides in early pregnancy and risk for gestational diabetes and preeclampsia among spouses of pesticide applicators, which provides some of the first evidence that these adverse pregnancy outcomes may have an environmental component.

Initiatives

Request for Applications (RFAs)

- **Neuroimmune Mechanisms and Chronic Fatigue Syndrome**
  The goal of this RFA, which was issued by the NIH ORWH and co-sponsored by several NIH IC's, including the NIEHS, is to solicit applications that support research on the neuroimmune mechanisms involved in the pathogenesis and pathophysiology of chronic fatigue syndrome and spectrum disorders in diverse groups and across the life span. (RFA-OD-06-002)
- **Building Interdisciplinary Research Careers in Women's Health (K12)**
  The NIH ORWH and co-sponsors, which include the NIEHS, invited institutional career development award applications for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Program. This program supports mentored research career development of junior faculty members, known as BIRCWH Scholars, who have recently completed clinical training or postdoctoral fellowships and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health or sex/gender factors. The goal of this RFA is to increase the number and skills of investigators through a mentored research and career development experience leading to an independent scientific career that will benefit the health of women, including research on sex/gender similarities or differences in biology, health, or disease. The program accomplishes these goals by ensuring that mentors represent diverse disciplines needed to carry out interdisciplinary projects that bridge career development/training with research independence for BIRCWH scholars. (RFA-OD-06-004)
- **Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50)**
  The ORWH and co-sponsors, which include the NIEHS, issued this RFA to promote interdisciplinary research in sex/gender factors through Specialized Centers of Interdisciplinary Research (SCOR). Each SCOR promotes interdisciplinary collaborations and develops a research agenda bridging basic and clinical research on sex/gender factors underlying a priority women's health issue. The SCOR program complements other federally supported programs addressing women's health issues. (RFA-OD-06-003)

Program Announcements (PAs)

- **Chronic Fatigue Syndrome: Pathophysiology and Treatment (R01, R03, R21)**
  These PAs were issued by the ORWH and co-sponsored by several NIH ICs, including the NIEHS. They are soliciting investigator-initiated applications that propose to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome, also known as myalgic encephalomyelitis, in diverse groups and across the life span. (PA-07-263, PA-07-264, PA-07-265)
- **In Utero Exposure to Bioactive Food Components and Mammary Cancer Risk (R01, R21)**
  These PAs solicit innovative preclinical research applications that will enhance the understanding of the relationship between exposures to bioactive food components and/or environmental chemicals in utero, hormonal and growth-factor response, gene expression or epigenetic changes, and subsequent mammary cancer risk in preclinical models. Although much evidence suggests that dietary components are linked to cancer prevention, the specific nutrients, sites of action, and role of exposure in utero remain elusive. Similarly, there are data suggesting a role for environmental agents, such as mycotoxins, heterocyclic amines, and

environmental chemicals with endocrine activity, in the etiology of mammary cancer. However, the doses, windows of susceptibility, and mechanisms are unclear. These PAs encourage applications that apply new high-throughput genomic, epigenomic, proteomic, and metabolomic technologies to determine how dietary exposures in utero influence adult breast cancer susceptibility. The resulting information will help define effective maternal dietary intervention strategies for breast cancer prevention in her offspring. (PA-07-187, PA-07-277)

Conferences and Workshops

- **Genomics, Endocrine Disruption, and Wildlife and Human Health**
  This conference was convened on May 23-27, 2005 in Boston, MA.
- **Environmental Solutions to Obesity in America's Youth**
  This meeting was convened on June 1-2, 2005 in the Washington, DC, Convention Center.
- **Lupus Conference**
  This conference was convened on September 8-9, 2005 in Washington, DC.
- **2nd Annual Obesity Conference: Implications for the Food and Drink Industry**
  This conference was convened on October 4-5, 2005 in Brussels, Belgium.
- **Emerging Topics in Breast Cancer and the Environment Research**
  This conference was convened on November 9-11, 2005 in East Lansing, MI.
- **Women's Health Research Day 2006**
  This conference was convened on April 4-5, 2006 at the University of North Carolina, Chapel Hill, NC.
- **Workshop on Lupus and the Environment**
  This workshop was convened on September 8-9, 2006 in Washington, DC.
- **Reproductive Tumors Workshop**
  This workshop was convened on May 22-24, 2006 in Raleigh, NC.
- **Environmental Causes of Breast Cancer Conference**
  This conference was convened on November 2-3, 2006 in Berkeley, CA.
- **Independent Panel to Evaluate Whether Genistein or Soy Formula is Hazardous to Human Development or Reproduction**
  This meeting was convened on March 15-17, 2006 in Alexandria, VA.

Health Disparities among Special Populations of Women

The following studies and findings are examples of NIEHS research that address health disparities in special populations of women. Additional information on many of these studies is provided above.

Polymorphisms in Nucleotide Excision Repair Genes Modify Breast Cancer Risk in Smokers

Breast cancer occurs at different rates in different racial groups. NIEHS-supported researchers determined that African American women smokers with specific combinations of polymorphisms in nucleotide excision repair genes are more susceptible to breast cancer than white women who smoke. The investigators claim that this is the first study to examine nucleotide excision repair polymorphisms as susceptibility factors for breast cancer in combination with smoking.

A Mitochondrial DNA Polymorphism is Associated with Invasive Breast Cancer in African American Women

NIEHS-supported investigators found an association between the 10398A allele and invasive breast cancer in African American women.

Birth Outcome Can Be Dependent on Balance of Pro- and Anti-inflammatory Cytokines

African American women with a specific genetic polymorphism for interleukin-4 had about a three-fold increase in the risk for spontaneous preterm birth. Maintaining the proper balance of pro- and anti-inflammatory cytokines is crucial for good pregnancy outcomes, and deviations in either direction may increase the likelihood of preterm birth or low birth-weight babies.

Uterine Fibroid Study

Uterine leiomyomas are the most common type of reproductive tract tumor in women. These benign smooth muscle tumors are the

primary cause for hysterectomy, with symptoms and complications related to uterine leiomyomas accounting for one-third of all hysterectomies in the U.S. About one-fifth of all gynecological-related hospital admissions are due to complications with uterine leiomyomas. The major complications are excessive uterine bleeding, pelvic pain, and infertility. Recent data suggest that fibroids can also cause pregnancy complications, such as placenta previa and breech presentation. Uterine leiomyomas are a significant health problem for women but particularly for African American women. A recently completed cross-sectional study of uterine leiomyomas (fibroids) in women age 35 to 49, who were randomly selected from members in a prepaid health plan in Washington, DC, showed a surprisingly high cumulative incidence of fibroids based on sonogram data. The prevalence of ultrasound-detected fibroids was about 80 percent for African American women and about 70 percent for Caucasian women. A substantial percentage of the women with fibroids were not previously diagnosed (44 percent and 69 percent for African Americans and Caucasians, respectively).

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 impact 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, the occupational roots of health disparities among women in a five-county region of northeastern North Carolina are being investigated.

Engaging Urban Residents in Assessing Neighborhood Environments

Researchers have worked to delineate the manner in which urban environments reflect broader social processes, such as those creating racially, ethnically, and economically segregated communities with vast differences in aspects of the built environment, opportunity structures, social environments, and environmental exposures. Interdisciplinary research is essential to gain an enhanced understanding of the complex relationships between these stressors and protective factors in urban environments and health. The purpose of this study was to examine the ways that multiple factors may intersect to influence the social and physical context and health within three areas of Detroit, MI. The findings from the stress process exercise used in the focus groups validated the relevance of a number of existing concepts and measures, suggested modifications of others, and evoked several new concepts and measures that may not have been captured without this process, all of which were subsequently included in the survey and environmental audit conducted by HEP. Including both qualitative and quantitative methods can enrich research and maximize the extent to which research questions being asked and hypotheses being tested are driven by the experiences of residents themselves. This information can enhance our efforts to identify strategies to improve the physical and social environments of urban areas and, in so doing, reduce inequities in health.

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 among socioeconomic status (SES), economic development, and CVD, the largest contributor to all-cause mortality in the U.S. 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 among 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 estimate the relationship among racial and ethnic group status, SES, and mental and physical health in a stratified, multistage probability sample of 1,000 adults in Detroit, MI. The study will also estimate the relationship among racial or ethnic group status, SES, and specific biomarkers for cardiovascular risk factors in a subset of this sample. In addition, it will examine the relationships between neighborhood, sociodemographic context, selected aspects of the physical environment, and selected aspects of the social environment; investigate independent and cumulative effects of exposure to psychosocial stressors on biological risk markers for CVD; document the strength of the association among airborne particulate matter and selected proximate risk and protective factors for CVD; investigate potential mediating and moderating effects of behavioral and psychosocial responses to stressors and micronutrient intake on the relationships between selected aspects of the physical and social environments and biological markers for CVD, and self-reported CVD and depression; and 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.

Exploration of Work and Health Disparities among Black Women Employed in Poultry Processing in the Rural South

An ongoing collaboration developed as academic investigators responded to a specific request from community members to document health effects on black women of employment in poultry-processing plants in rural North Carolina. Primary outcomes of interest are upper extremity musculoskeletal disorders and function as well as quality of life. Because of concerns for community women and the history of poor labor relations, a longitudinal study was conducted in a manner that did not require involvement of the employer. To provide more detailed insights into the effects of this type of employment, the epidemiologic analyses are supplemented by ethnographic interviews. The resulting approach requires community collaboration. Community-based staff, as paid members of the research team, manages the local project office, recruits and retains participants, conducts interviews, coordinates physical assessments, and participates in outreach. Other community members assisted in the design of the data collection tools and the recruitment of longitudinal study participants. They also took part in the ethnographic component of the study. This is an example of a model through which academic researchers and community members can work together productively under challenging circumstances. Notable accomplishments include the recruitment and retention of a cohort of low-income rural black women, often considered hard to reach in research studies. This community-based project includes a number of elements associated with community-based participatory research.

Systemic Lupus Erythematosus: The Carolina Lupus Study

This project focuses on understudied diseases that particularly impact women and minority populations. Autoimmune diseases are chronic, disabling conditions, and as a group they represent a leading cause of death among women younger than age 65 years. The NIH estimates that 5 to 8 percent (14-22 million people) in the U.S. suffer from these diseases. Despite the burden of autoimmune diseases, there has been relatively little epidemiologic research into their etiology. Autoimmune diseases are more common in women than in men, and, in some of these diseases, such as systemic lupus erythematosus, more than 85 percent of patients are female. Compared with whites, African Americans are three to four times more likely to develop lupus. This research will advance our understanding of modifiable risk factors and the etiologic pathways involved in lupus. Lupus is a potential model for autoimmune diseases in general and a model for complex diseases that involve not just genetic factors but also genetic, hormonal, and environmental interactions. This research also examines common and modifiable risk factors (i.e., diet) using well-validated prospectively collected data.

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 women with breast cancer. The reasons will most likely prove to be multifactorial. A recently published study supported by the NIEHS provides new evidence that variation in the mitochondrial genome contributes to breast cancer susceptibility. This variation may underlie differences in the incidence of breast cancer between African American and white women. The magnitude of the risk associated with the 10398A allele suggests that this polymorphism is an important new risk factor to consider in the etiology of breast cancer in African American women. Environmental exposures might play a role. A 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, they would be at higher risk for breast cancer. The NIEHS, in partnership with the NCI, has supported 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.

Gender Analysis

Gender Differences in Mouse Airway Responsiveness to Lung Injury

The roles of gender and sex hormones in lung function and disease are complex and not completely understood. NIEHS-supported researchers examined the influence of gender on lung function and respiratory mechanics in naive mice and on acute airway inflammation and hyperresponsiveness induced by intratracheal lipopolysaccharide (LPS) administration. The study found evidence that androgen in males at physiologic levels or in females receiving exogenous hormone significantly affected airway response as determined by analysis of lung function, assessment of LPS-induced airway inflammation, lung histopathology, and immunoblotting. Castrated males, males receiving anti-androgen pellets, and intact females were less responsive to lung injury than intact males and androgen-treated females. Ovariectomized females responded to lung injury in ways similar to those shown in sham-operated females. Researchers also demonstrated that the severity of hypothermia in response to LPS was affected by gender. There were no significant differences found attributable to mouse strain. The NIEHS researchers stated that their data suggest the importance of carefully considering gender in the design of murine studies of the pulmonary effects of LPS. An important contribution of this study is its indepth investigation of the role of androgens, a factor not addressed in earlier studies. Based on the results of their study, the NIEHS researchers concluded that sex hormones may provide novel targets for therapeutic intervention in inflammatory lung disease.

NTP Scientists Help New Treatment Enter Clinical Trials

National Toxicology Program researchers have collaborated in a detailed toxicity and biodistribution analysis that has moved a novel gene transfer treatment protocol closer to clinical trial. The health of 200 adult male and female rats, divided into four experimental groups per gender, was monitored over a 92-day period. Animals in the test groups received injections of the virus containing the gene for aquaporin-1 into the submandibular duct. For toxicity determination purposes, the treatment dose was approximately 10 times the corresponding lowest and highest doses proposed for clinical study. No clinical or gross pathological signs of adverse toxicological effects in animals were seen after gene transfer. There were no treatment-associated losses of animals. Animals in all groups continued to thrive after treatment, with normal patterns of weight gain and food and water consumption. Except for local, dose-dependent inflammatory changes in the targeted gland, animals showed no severe or permanent damage to the salivary gland and limited vector distribution elsewhere in the body. However, three mild gender-related response differences were seen. Female, but not male, rats exhibited small reductions in food consumption and body weight gain and

had evidence of persistent inflammation after vector treatment. Despite some gender differences in response to treatment, clinical chemistry indicators of major organ function were normal for all animals.

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

The NIEHS participates in this RFA, which was issued by the NIH ORWH and other NIH ICs. This RFA seeks to promote interdisciplinary research in sex/gender factors through Specialized Centers of Interdisciplinary Research (SCOR).

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. For example, 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 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. Accomplishments in this area are described below.

Accomplishments

Estrogen-related Research

Several NIGMS investigators study metabolic enzymes that control estrogen levels. Estrogens are required for normal growth and maturation of ovarian follicles. Kimberly Barnett, a predoctoral investigator from the University of Maryland is investigating how the aryl hydrocarbon receptor affects folliculogenesis via mechanisms involving estrogen steroidogenesis. Sulfate conjugation reactions are critical in the biotransformation of steroid hormones, neurotransmitters, and several drugs. Sulfation reactions are catalyzed by cytosolic sulfotransferases (SULTs). Dr. Rebecca Blanchard at the Fox Chase Cancer Center recently identified three common SULT1A1 alleles with different frequencies in Caucasian and African American populations. Investigators will analyze the association between these alleles and specific breast cancer characteristics in a cohort of 600 Caucasian and African American women with breast cancer. The results will increase our understanding of the contribution of SULT1A1 pharmacogenetics to individual variation in response to estrogens and an important antiestrogen. In yet another NIGMS-supported project, Dr. Mary Vore at the University of Kentucky is looking at drug metabolism in pregnancy and the effects of estrogens on transporter control.

Fertility-related Research

Research conducted by Dr. Steven Rosen at University of California, San Francisco is extending the pioneering work conducted at that institution on L-selectins to demonstrate their presence on trophoblast cells of the blastocyst. Investigators 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.

Autoimmune Research

A number of NIGMS investigators conduct studies related to mechanisms underlying autoimmune diseases. Research conducted at the National Jewish Medical and Research Center by Dr. Gongyi Zhang determined how Tall-1, a protein that 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 matu-

ration that seems to contribute to lupus. Dr. Gary Glick at the University of Michigan has identified a new benzodiazepine that is remarkably effective in treating a lupus-like disease in the two most clinically relevant polyclonal animal models of systemic lupus erythematosus. Significantly, this treatment is not accompanied by the broad toxicities and side effects that plague current therapeutic regimes.

Other Research and Research Training

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 disproportionately affecting 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 at the State University of New York at Stoney Brook 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. Dr. Gary Keck at the University of Utah is completing ongoing studies on the promising compound, epothilone, which exhibits activity similar to that of taxol. Studies of second-generation taxoids continue to hold promise.

Interindividual drug responses depend on genetic variation as well as modifying factors, such as the environment, diet, other medications, age, and gender. Under a program announcement titled Mechanisms Underlying Individual Variations in Drug Response, the NIGMS supported 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 titled Pharmacogenetic Research Network and Database have built on this research by supporting the formation of a coordinated Pharmacogenetic Research Network and Database. Dr. David Flockhart, 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. This study, which was published in the Journal of the National Cancer Institute, suggests that metabolism of tamoxifen may be modified by the genetic makeup of the person taking the drug. In addition, this research 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 among patients.

The NIGMS has supported extensively interdisciplinary research training of predoctoral and postdoctoral scientists. The Medical Scientist Training Program (MSTP) provides training of students with both a medical and scientific background. 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 they will be able to relate their results to clinical areas. The predoctoral training programs 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 disease. 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 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 Web site at 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 and eating disorders than boys, while boys are more likely to suffer from autism and attention deficit disorder. 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, some women are at increased risk of depression during certain times of reproductive change, such as during the perinatal period.

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. To achieve this goal, the NIMH has offices and groups designated to focus on women's mental health. The Women's Mental Health Program is located in the Office for Special Populations within the Office of the NIMH Director. The women's mental health program 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 the liaison with the NIH ORWH 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. This Office coordinates NIMH activities that 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 the NIMH scientific activities related to women's health and sex/gender differences research. Members of the team include representatives from all five extramural research divisions and the Offices of Science Policy, Planning and Communications, Constituency Relations and Public Liaison, and the Executive Office. Team members work across disciplinary boundaries to plan workshops, prepare and review science reports, and create program announcements related to women's mental health.

In addition to increasing scientific information on sex and gender differences, the NIMH has advanced knowledge in the area of specific mental disorders that either effect women exclusively (e.g., perinatal depression) or predominantly (e.g., eating disorders). Through cross-cutting programs, such as the Women's Mental Health Team, the NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and the prevention of mental disorders in women. This report highlights accomplishments, papers on sex differences and women's mental health research, specific initiatives to promote research in this area, efforts on behalf of special populations of women, as well as specific initiatives in the area of sex/gender differences research. Research highlights are grouped by three major subheadings: Research on Sex Differences in Brain and Behavior, Research on Specific Mental Disorders, and Research on AIDS and Mental Health Disparities.

Accomplishments

Research on Sex Differences in Brain and Behavior

Many mental disorders have striking gender disparities in prevalence, as shown in population-based epidemiology studies of adults in the U.S. 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.

Stress Affects the Quality of Parental Care in a Sex-specific Manner

As shown in an animal species (voles) in which both parents participate in care of their offspring, stress experienced by adults affects their ability to care for offspring differently, depending on the sex of the parent. Prairie voles are one of a very limited number of animal species in which both sexes participate in the rearing of offspring. In addition, male and female prairie voles form life-long pair bonds with partners. As such, they are an extremely valuable model system for examining the neural systems underlying the formation of social bonds of various types. In the present study, male and female prairie voles were exposed to an acute stressor, and then behavioral measures of the level of their parental care were assessed, along with their reaction to the stressor using measures of corticosterone, a hormone released by the adrenal glands in response to stress. Interestingly, the investigators noted that following the stress experience, male voles responded with an increased level of parental care while female voles showed no changes. The investigators hypothesize that male prairie voles may use social contact to modulate stressful experiences whereas females do not. The investigators suggest that this is an important area to study in the future. This study demonstrates a sexually dimorphic response to stress and the modulating effect of social interactions, which may be of importance in understanding sex differences in mental disorders. (Bates, K.L., et al. *Physiology and Behavior* 87:424-420, 2006)

Neonatal Activation of Estrogen Receptors by Dopamine Influences Subsequent Social Behavior

Activation of gonadal steroid receptors in the developing brain is responsible for the organization of a variety of sex differences that persist throughout the life span. It is known that steroid receptors can be activated in both ligand-dependent and ligand-independent manners. For example, ligand-independent activation of estrogen receptors (ER) occurs when they are activated in the absence of the ligand, estrogen. This report provides the first evidence of dopamine-receptor mediated, ligand-independent activation of ERa in the developing brain. It is well established

that activation of estrogen receptors increases the progesterone receptor. Administering a dopamine receptor agonist (SKF38393) to neonatal rats increased the expression of the progesterone receptor (PR) in the bed nucleus of the stria terminalis and the central amygdala. Prior treatment with an ER antagonist prevented the PR increase, thus indicating that dopamine activates estrogen receptors in specific regions of the developing brain to increase PR. It is known that the bed nucleus of the stria terminalis and the central amygdala play a role in the development of social behavior. Interestingly, the present study also found that animals treated with the dopamine agonist showed higher levels of social play behavior and that this is due to ER activation. Thus, ligand-independent activation of ER neonatally by dopamine appears to organize the circuitry that controls one kind of social behavior. (Olesen, K.M., et al. *Endocrinology* 146:3705-3712, 2005)

Genes on Sex Chromosomes Influence Expression of Social Behavior in Mice

Studies of humans and animals have revealed gender differences in expression of some types of social behaviors. Typically, males are more aggressive, and females show more parental behavior. In this study, Dr. Gatewood and colleagues at the University of Virginia separated the gene for male gonadal development from other genes present on the sex chromosomes and "knocked it out," resulting in mice that had female gonads but otherwise were genetically male with all of the remaining Y (male) chromosome genes. This enabled the researchers to examine whether gender-related differences in social behavior are driven solely by differences in hormones produced by the gonads, or whether other genes on sex chromosomes play a role. The knockout mice were more similar to intact, unaltered male mice than to female mice in their aggression and parental behavior. This suggests that additional genes on the Y chromosome (that is, genes other than that responsible for gonad development) are important in the determination of sexually differentiated social behavior. Because many mental disorders are characterized by social deficits, understanding the genes involved in social behavior is important in understanding the biological basis of these deficits. (Gatewood, J.D., et al. *The Journal of Neuroscience* 26:2335-2342, 2006)

Sex Differences in the Stress Responsiveness of the Brain Noradrenergic System

Activation of the locus coeruleus (LC)-norepinephrine (NE) system is an important component of the stress response. This study compared LC responses to stress in female and male rats under different hormonal conditions. Basal electrophysiological response rates in the LC were similar between groups. However, the magnitude of LC activation elicited by hypotensive stress was substantially greater in females, regardless of hormonal status. The difference in stress sensitivity could be attributed to the differential postsynaptic sensitivity of LC neurons to corticotropin-releasing factor (CRF), which mediates LC activation by hypotension. CRF was 10 to 30 times more potent in activating LC neurons in female than male rats. Interestingly, previous exposure to swim stress differentially regulated LC responses to CRF by sensitizing LC neurons to CRF in male but not female rats. The net effect of this was to abolish sex differences in LC sensitivity. Finally, CRF receptor (CRF-R) protein levels in the LC were greater in ovariectomized female than male rats. This is the first study to demonstrate sex differences in the stress responsiveness of the brain noradrenergic system. These sex differences in the CRF regulation of the LC-NE system translate to a differential response to stress and may play a role in the increased vulnerability of females to stress-related psychiatric disorders. (Curtis, A.L., et al. *Neuropsychopharmacology* 31:544-554, 2006)

Estrogen Can Interfere with the Extinction of Fear Memories

Impairments in the ability to extinguish a previously conditioned fear response when the fearful stimulus no longer predicts an aversive event have been associated with increased risk for anxiety disorders and can interfere with the treatment of fear-related disorders. Anxiety disorders have been shown to be more prevalent in women, yet prior studies of extinction and extinction memory in humans have not examined whether there are differences in these capacities between men and women. A

recent NIMH-supported study examined the influence of gender and menstrual cycle on the ability to extinguish a conditioned fear memory and recall this extinction training a day later. First, the researchers paired a neutral stimulus with a small but annoying shock to the fingers and measured skin conductance response, a physiological measure correlated with arousal and the experience of fear. Following this, extinction training was conducted where the stimulus was presented without the subsequent shock. Recall of this extinction training was tested a day later by again presenting the stimulus without the shock and measuring the skin conductance response. During the initial acquisition of the fear conditioning, men showed greater fear responses relative to women. However, there were no differences between males and females in their ability to acquire extinction learning. In contrast, when tested a day later for extinction recall, males and females in the early part of their menstrual cycle (when estrogen levels are low) had better extinction memory than females at mid-cycle when estrogen levels are much higher. These results indicate that high levels of estrogen can interfere with the ability to recall the extinction of previously fearful memories and point to the importance of exploring the influence of estrogen on the brain regions implicated in extinction memory. These results also highlight the importance of knowing what phase of the menstrual cycle a women is in when studying learning and memory processes, particularly as they relate to fear. (Milad, M.R., et al. *Behavioral Neuroscience* 120:1196-1203, 2006)

Motherhood Can Reduce the Effects of Stress on Learning

Women respond more to stressful experiences than men and are more likely to suffer from stress-related illnesses. Previous animal studies have demonstrated that acute stress can improve learning in males but often impairs learning in females, particularly during the portion of their life span when they are reproductively viable. Other studies have shown that females may be less responsive to stressful events during pregnancy. A recent NIMH-supported study examined the effects of stress on learning during pregnancy and during the postpartum period to assess whether changes in hormonal state and/or maternal behavior can protect against the negative effects of stress on learning. The investigators measured the effects of several different types of short-term stressors (shock, restraint, forced swim) on the ability to learn to blink in response to a tone that signals the delivery of a puff of air to the eye. They tested the effects of stress on this form of learning in virgin, pregnant, and postpartum rats. The results show that all of the forms of stress decreased the ability to learn the eye-blink response in both virgin and pregnant rats but had no effect on learning in postpartum rats. To determine whether hormonal state following pregnancy or the presence of rat pups was the key factor protecting postpartum females from the effects of stress, the researchers then tested the effects of stress in postpartum rats separated from their pups and in virgin animals induced to show maternal behavior through exposure to rat pups. They found that postpartum females that were separated from their pups showed impairments in learning following stress whereas virgins expressing maternal behavior showed no detrimental effects of stress on learning. Together, these results demonstrate that the effects of stress on learning in females is significantly influenced by both reproductive status and the expression of maternal behavior and that motherhood can mitigate the negative effects of stress on learning. This may be an adaptation that increases the likelihood that the mother and her offspring will survive. (Leuner, B. and Shors, T.J. *Hormones and Behavior* 50:38-51, 2006)

Sex Differences in Brain Development Parallel Sex Differences in Susceptibility to Develop Autism

Recent research suggests a sex difference in individuals diagnosed with autism in the development of a brain region thought to be critical in the processing of social and emotional information. Autism is a very serious disorder that becomes apparent early in development. It is characterized by a variety of symptoms, including deficits in social processing, communication, and motor activity (repetitive behavior). The present report investigates a brain region (the amygdala) that is important in the processing of social and emotional information. This report follows up on an earlier published study from this laboratory that suggested that,

in boys diagnosed with autism, the amygdala undergoes an unusually early spurt in development, reaching adult size well before that of the amygdala in normal (control) subjects. In the current study, the investigators carefully compared the amygdalas from adults diagnosed with autism and control subjects to understand the exact nature of any differences. In brain samples obtained from subjects who had died from a variety of natural causes, the investigators carefully measured the size of the different subregions of the amygdala, counted the number of cells in each of these subregions, and compared the results of normal subjects with those diagnosed with autism. They found no difference in either the overall size of the amygdala or individual subregions or in the average size of individual neurons within the amygdala. However, they did find that there was a significant decrease in the number of cells overall in the amygdale, specifically in one subregion called the lateral nucleus. The findings from this carefully conducted study are important in helping to establish the specific pathophysiology underlying autism. An important next step is to understand the relationship between this finding and their earlier observation about an abnormally early growth in size in the amygdala in boys diagnosed with autism. Understanding how the brain is altered by this disease is critical to ultimately establishing the underlying cause for autism. (Schumann, C.M. and Amaral, D.G. *The Journal of Neuroscience* 26:7674-7679, 2006)

Exposure to Estrogen during Development Protects against the Effect of Estrogen on Spatial Learning in Adult Females

The investigators previously reported that high doses of estrogen administered before and during learning of a spatial memory task impairs learning in adult ovariectomized female mice but not in adult male mice. In the present study, the investigators test the hypothesis that neonatal exposure to estrogen may protect against this impairment. Male and female animals were treated neonatally with estrogen or vehicle (oil), were gonadectomized as adults, and then were treated with estrogen or vehicle (oil) before and during training on the spatial memory task. The results show that females given estrogen as neonates and then again as adults do not show the learning impairment seen in females given vehicle as neonates and then estrogen as adults. These results support the hypothesis that estrogen exposure during the neonatal period contributes to sex differences observed in spatial learning. Moreover, these observations suggest that the timing of estrogen exposure is critical for the organization of brain regions important for learning and memory. (Imwalle, D.B., et al. *Hormones and Behavior* 50:693-698, 2006)

High Circulating Estrogen Impairs Working Memory

This study examined the effects of restraint stress on a memory function regulated by the prefrontal cortex (PFC) in both male rats and cycling female rats in either the proestrus (high estrogen) or estrus (low estrogen) phase of the estrous cycle. Animals were restrained for 60 or 120 minutes and then tested on spatial delayed alternation, a PFC-mediated working memory test. Results revealed that 60 minutes of restraint only impaired females in proestrus, while 120 minutes of restraint produced significant impairments in all animals. These results demonstrate an interaction between hormonal status and cognitive response to stress in female rats, with high estrogen levels being associated with amplified sensitivity to stress. Overall, the results suggest ovarian hormone influences on PFC-mediated effects of stress on cognitive function. (Shansky, R.M., et al. *Behavioral and Brain Functions* 7:2-8, 2006)

Repeated, Long Separation from Pups Produces Depression-like Behavior in Rat Mothers

The effects of maternal separation on the offspring have been commonly studied by employing animal models of maternal separation as a paradigm for depression, loss, and anxiety. However, until recently, there were no animal models of maternal depression. The current study explores the idea that repeated intervals of maternal separation from pups will produce a depression-like state in mothers induced by learned helplessness, which results from the inability to control access to pups. Mothers and pups were exposed to periods of long separation, brief separation, or no separation from postpartum day two to 14. Results from the forced swim test, which

provides a measure of depression, demonstrate that repeated long separation for three hours per day produces a higher rate of immobility in these mothers when compared with those that experienced either no or brief separation. As this difference was observed on both first and second day of testing, the finding suggests that the experience of long-term separation from pups induces a depression-like learned helplessness. In addition, mothers that display depression-like behavior tend to lick their pups less than mothers from the other two groups. These novel findings suggest that rapid onset of depression may be induced by disruption of the attachment relationship between mothers and their offspring. Unlike previous animal models of depression that involved exposure of animals to chronic, inescapable, or unpredictable stress, this may be the first model of animal depression that is induced by disruption of a social relationship. Because human depression often involves disruption, loss of, or disturbance in significant social relationships, this model could provide new ways to investigate short and long-term outcomes of postpartum depression in both mothers and their offspring. (Boccia, M.L., et al. *Psychoneuroendocrinology* 32:65-71, 2007)

Estrogen Selectively Modifies Serotonin Synthesis in the Brain

Previous studies in rodents and non-human primates have demonstrated increased serotonin (5HT) synthesis by estrogen. The current report examined the regulation by estrogen of the brain-specific isoform of rat tryptophan hydroxylase (TPH2), an important enzyme controlling 5HT levels in the brain across subregions of the 5HT-containing raphe nucleus. Chronic estrogen treatment of ovariectomized (OVX) rats produced highly selective changes in TPH2 mRNA expression in the midbrain raphe with increased mRNA in the caudal dorsal raphe nucleus. Interestingly, combined estrogen and progesterone treatment did not change TPH2 mRNA relative to ovariectomized controls. The second main finding of this study was that TPH2 mRNA levels in some subregions of the dorsal raphe nucleus correlated with anxiety-like behavior in the open field test. These results are consistent with another recent behavioral study by the same group showing that estrogen-treated OVX rats showed less anxiety-like behavior in the open field than either OVX or OVX rats given both estrogen and progesterone. These results suggest that differential actions of estrogen on 5HT-mediated anxiety behavior may relate to its selective effects on subpopulations of 5HT neurons. Additional work is necessary to determine the mechanisms by which this differential effect of estrogen and progesterone may occur. (Hiroi, R., et al. B*iological Psychiatry* 60:288-295, 2006; Hiroi, R., et al. *Behavioral Brain Research* 166:93-100, 2006)

Estrogen Regulates Transcription Factors Modulating Anxiety and Cognition

Estrogen (E) induces dendritic growth and proliferation of new neurons in the adult hippocampus. The similarity between E actions and those of brain-derived neurotrophic factor (BDNF) suggest that this neurotrophic factor may be a likely candidate to mediate the effects of E on some of the growth-related processes in neurons and synapses. The gene encoding BDNF contains a sequence similar to an E-response element found in E-target genes, suggesting E actions on BDNF may result from a direct, genomic effect. However, E may also modulate the expression of BDNF as a consequence of activation of the cAMP response element-binding protein (CREB) via specific molecular signaling cascades. Results indicated 20 to 39 percent increases in protein levels of CREB, pCREB, BDNF, and mRNA levels of BDNF mRNA in the medial amygdala and hippocampus of rats given E for 14 days. Previous results suggest that changes in these signaling molecules can induce behavioral changes. The ability of E to regulate various components of CREB signaling and BDNF in specific limbic brain regions suggests that estrogen is able to modulate subtleties of neuronal function that are involved in complex behaviors. (Ahou, J., et al. *Neuroendocrinology* 81:294-310, 2005)

Research on Specific Mental Disorders

Certain mental disorders are more prevalent in women than men. Mood disorders, anxiety disorders, eating disorders, and certain types of personality disorders (such as borderline personality disorder) are all more common in women than men. According to the National

Comorbidity Replication Study, approximately 24.9 percent of women will experience a mood disorder, and 36.3 percent will experience an anxiety disorder at some time during their lives. By early adolescence, gender differences in the incidence of major depression and anxiety disorders are evident. Eating disorders, although less common than mood and anxiety disorders, are associated with severe metabolic consequences that can be life threatening. Genetic and hormonal factors, sex differences in stress response, and risk factor exposures have all been implicated in gender disparities in these disorders. Although these disorders are clinically distinct, they often co-occur and are thought to share some etiological factors. Additionally, some women are vulnerable to developing these disorders at times of reproductive change, such as during the perinatal period or the menopausal transition.

The NIMH funds a wide range research to enhance understanding of these mental disorders. 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. The following is a sample of NIMH research highlights from studies on specific mental disorders.

Relapse of Major Depression during Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment

Contrary to a common belief that the hormonal changes associated with pregnancy provide a protective effect against depression, women with major depression who discontinue antidepressant medication during pregnancy are at risk of relapse, according to a study by Dr. Lee Cohen and colleagues. This study was conducted to determine the risk of relapse in pregnant women with major depression who discontinued or who attempted to discontinue antidepressant medication close to conception compared with those who maintained treatment with these medications. The researchers found that 43 percent of women in the sample relapsed during pregnancy, and half of those relapsed during the first trimester. Among women who maintained their medication throughout the pregnancy, 26 percent relapsed compared with 68 percent of those who discontinued their medication. With greater awareness and increased treatment of depression in the community, growing numbers of women may face a clinical decision regarding use of antidepressant medication during pregnancy. Navigating this clinical course can be facilitated by the accurate delineation of the relative risks of prenatal exposure to medication on the one hand and the risk of relapse of psychiatric disorder on the other. Quantification of these risks affords clinicians the opportunity to make collaborative treatment decisions consistent with individual needs and wishes. Such information can also help to refine treatment guidelines for women with a history of depression who are planning to conceive or who experience mood disorders during pregnancy. (Cohen, L.S., et al. The *Journal of the American Medical Association* 295:499-507, 2006)

A Preventive Intervention for Pregnant Women on Public Assistance and at Risk for Postpartum Depression

Postpartum depression (PPD) is increasingly recognized as an illness with significant morbidity for women and their offspring. Women of lower income status seem to be at greater risk for PPD and may also face greater health care access issues. Depression during pregnancy is one of the strongest predictors of PPD, so the prevention of depression in pregnancy is seen as a promising intervention to reduce PPD. Dr. Zlotnick and colleagues tested a preventive intervention based on interpersonal psychotherapy that has been proven to be an effective treatment in non-pregnant women. They compared this intervention with treatment as usual among 99 ethnically diverse women who were at risk for PPD and receiving public assistance. Four 60-minute group sessions were offered with an individual booster session provided after delivery. Forty-six women in the intervention and 40 in the treatment as usual condition were compared at three months after delivery. Two (4 percent) of the intervention women and eight (20 percent) of the treatment as usual condition developed postpartum depression, suggesting that further development of this preventive intervention holds significant promise in reducing postpartum depression in this high-risk group. (Zlotnick, C., et al. *American Journal of Psychiatry* 163:1443-1445, 2006)

Risk for New Onset of Depression during the Menopausal Transition

Investigators prospectively studied a group of healthy women ages 36 to 45 over a 36-month period and examined the incidence of new onset depression through structured clinical interview and depression ratings. They also assessed menstrual cycle status. None of the women had a previous history of depression. Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, even after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms. (Cohen, L.S., et al. A*rchives of General Psychiatry* 63:385-390, 2006)

Prior Depression Has Long-term Effects on Women's Health and Functioning in Mid-life

As a part of a large community-based, multiethnic study of African American, Hispanic, and white women as they transitioned through menopause, researchers were interested in understanding the long-term effects of a history of depression, independent of current depression, on current physical and mental health as well as social and interpersonal functioning. They found that women with a history of depression, which did not vary among racial/ethnic groups, were more likely to currently experience a variety of physical and negative mood symptoms, sleep problems, body pain, and impaired social and interpersonal functioning. There was no consistent pattern of differences in poor health outcomes among those with minor depression or major depression single episode. There was a linear relationship between prior depression severity and prevalence of current physical symptoms, but women who had experienced minor depression or a single episode of depression experienced physical symptoms and poor functioning at similar rates. The findings underscore the importance of prior depression, including minor depression, in the absence of a current mood disorder and suggest that the impact of prior history on health outcomes should not be underestimated. (Bromberger, J.T., et al. *General Hospital Psychiatry* 27:200-208, 2005)

Fetal Lithium Exposure Increases Perinatal Complications

Lithium, a common treatment for bipolar disorder, has been used during pregnancy for more than four decades, but measurements of fetal lithium exposure and clinical consequences of such exposure are limited. The objectives of this study were to measure the rate of passage of lithium across the placenta, assess any association between plasma concentration of lithium at delivery and adverse perinatal events, and determine whether lithium concentrations can be reduced by briefly suspending therapy shortly before delivery. Maternal blood and umbilical cord blood were obtained at delivery to assay of lithium concentrations, and obstetrical outcome data were collected prospectively for 10 participants. Results show that lithium completely crosses the placenta and that higher lithium concentrations in infants are associated with more perinatal complications, such as lower Apgar scores, longer hospital stays, and higher rates of central nervous system and neuromuscular complications. Withholding lithium therapy for 24 to 48 hours before delivery resulted in a reduction in maternal lithium concentration, which could reduce the negative effects of the drug on fetal outcomes at delivery. Based on these data, the investigators have proposed treatment guidelines to improve neonatal well-being when lithium use is indicated in late pregnancy. (Newport, D.J., et al. *American Journal of Psychiatry* 162:2162-2170, 2005)

Children Benefit from Treatment of Maternal Depression

Major depressive disorder is highly prevalent. Often it is also a familial disorder. Children of depressed parents have high rates of anxiety, disruptive behavior, and depressive disorders that begin early, impair social functioning, and often continue into adulthood. Dr. Weissman and colleagues recently reported that effective treatment of maternal depression is associated with a reduction of symptoms and diagnoses in their children. They studied 151 mother-child pairs in eight primary care and 11 psychiatric outpatient clinics across seven regional

centers in the U.S. The depressed mothers were treated with medication as part of the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial. The children, between seven and 17 years of age, were assessed before initiation of their mothers' treatment (baseline) and then followed at three-month intervals. Remission of maternal depression after three months was associated with reductions in the children's diagnoses and symptoms. There was an overall 11 percent decrease in rates of diagnoses in children of mothers whose depression remitted, compared with an 8 percent increase in rates of diagnoses in children of mothers whose depression did not remit. Considering only the children with a diagnosis at baseline, remission was reported in 33 percent of those whose mothers had remitted, compared with only a 12 percent remission rate among children of mothers whose depression did not remit. All children of mothers whose depression remitted after treatment and who themselves had no baseline diagnosis for depression remained free of psychiatric diagnoses at three months, whereas 17 percent of the children whose mothers remained depressed acquired a diagnosis. The findings were similar for child symptoms. This report suggests that the benefit of treatment for depressed women extends to their children and highlights the importance of evaluating the children of depressed women in treatment, especially those whose mothers continue to be depressed. (Weissman, M.M., et al. *The Journal of the American Medical Association* 295:1389-1398, 2006)

Interpersonal Stress Exposure and Reactivity Contributes to Female Preponderance of Adolescent Depression

The emergence of sex differences in depression during adolescence has been well documented. However, the specific factors and processes that increase risk among adolescent girls remain elusive. In a recent study, Dr. Brennan and colleagues examined sex differences in stress exposure and reactivity to chronic and episodic stress in an attempt to elucidate these factors. They studied 816 youth (mean age 15 years, two months) selected from a birth cohort in Australia based on high and low maternal depression ratings. Adolescents and mothers were interviewed about episodes of depression and experiences with chronic and episodic stress. Girls reported higher levels of exposure to total episodic and interpersonal episodic stress. In contrast, boys reported higher levels of exposure to academic and close friendship chronic stress. Chronic stress was a significant predictor of depression in both boys and girls but did not predict sex differences in the likelihood of depression. However, higher rates of depression among girls were explained by greater exposure and greater reactivity to episodic stress, particularly interpersonal episodic stress. This report highlights the significance of episodic stress in explaining sex differences in depression. Because episodic events in the interpersonal domain are often modifiable, these findings have implications for intervention development. (Shih, J.H., et al. *Journal of Clinical Child and Adolescent Psychology* 35:103-115, 2006)

Negative Self-perceptions Partially Explain Female Preponderance of Adolescent Depression

Women are two to three times more likely than men to become depressed. The sex difference in rates of depression emerges during adolescence. A recent study by Dr. Brennan and colleagues examined factors that may explain this greater vulnerability for depression among adolescent girls versus boys. They studied 816 youth (mean age 15 years two months) selected from a birth cohort in Australia based on high and low maternal depression ratings. Adolescents, mothers, and fathers were interviewed about episodes of depression, the parent-child relationship, and adolescent attachment cognitions and self-perceptions. The study found that the factors associated with depression in adolescent boys and girls were generally similar and that girls were not more susceptible to the risk factors examined. However, girls reported higher levels of negative self-perceptions of achievement, self-worth, and physical appearance. These negative self-perceptions, in turn, partially explained girls' higher rates of depression. In the interpersonal domain, girls reported more positive self-perceptions and served as a source of protection against depression. This report suggests that adolescent girls' overall higher level of negative self-perceptions may partially explain the female preponderance

of depression during adolescence. (Eberhart, N.K., et al. *Journal of Abnormal Child Psychology* 34:495-508, 2006)

Prevention of Eating Disorders in At-risk College-age Women

The risk of developing an eating disorder can be reduced by an effective preventive intervention in young women. NIMH-funded researchers reported that an Internet-based intervention aimed at college-age women at high risk for developing an eating disorder was successful in reducing the weight and shape concerns of these women for up to two years and decreasing the risk for the onset of eating disorders. This was the first study to report that eating disorders can be prevented in high-risk women. (Taylor, C.B., et al. *Archives of General Psychiatry* 63:881-888, 2006)

Fluoxetine after Weight Restoration in Anorexia Nervosa: A Randomized Controlled Trial

The benefit of medication treatment in anorexia nervosa after weight restoration remains unproven. A critical step in the treatment of patients with anorexia nervosa is to maintain weight after weight restoration and thus prevent recurrence of the illness. Unfortunately, recurrence is common in anorexia nervosa. Antidepressant medications with serotonin activity, such as fluoxetine (Prozac) have been proposed as treatment to maintain remission and prevent recurrence in anorexia nervosa. A recently published controlled study conducted by NIMH-funded researchers, however, failed to find any efficacy in using fluoxetine after weight restoration in about 50 women (mean age 22 years) with anorexia nervosa. (Walsh, B.T., et al. *The Journal of the American Medical Association* 295:2605-2612, 2006)

Two-year Randomized Controlled Trial and Followup of Dialectical Behavior Therapy vs. Therapy by Experts for Suicidal Behaviors and Borderline Personality Disorder

Borderline personality disorder is a difficult-to-treat mental illness affecting up to 2 percent of adults (5.8 to 8.7 million Americans), most of whom are young women. People with this disorder of emotion regulation experience intense bouts of anger, depression, and anxiety that may last only hours, often in response to perceived rejection. They typically have tumultuous work and family life and may engage in risky, impulsive behaviors. Cutting, burning, and other forms of self-harm are common, with up to 9 percent ultimately committing suicide. Although they account for at least 20 percent of psychiatric inpatient admissions and frequently seek mental health services, patients with the disorder often fail to respond to commonly available treatments. Dr. Linehan and colleagues developed Dialectical Behavior Therapy (DBT), a variation on cognitive behavioral therapy that specifically targets suicidal behavior, behaviors that interfere with treatment, and risky social behaviors. The DBT was compared to psychotherapy treatment by non-behavioral therapist experts (TBE). The risk of dropping out of therapy was nearly three times higher among the TBE group; 59 percent dropped their first assigned therapist, compared with 25 percent of DBT patients. While there were no suicide deaths in the study, 46.7 percent of the TBE and 23.1 percent of the DBT patients attempted suicide during the study year. Among TBE patients, 57.8 percent visited emergency rooms for psychiatric problems, compared with 43.1 percent among DBT patients; 48.9 percent of TBE patients had at least one psychiatric hospitalization, often for suicidal thoughts, in contrast to 19.6 percent of DBT patients. (Linehan, M.M., et al. *Archives of General Psychiatry* 63:757-766, 2006)

Research on Health Behavior, AIDS, and Mental Health Disparities

A landmark 2001 Surgeon General's Report, titled Culture, Race, and Ethnicity, highlighted disparities in mental health services for racial and ethnic minorities in the U.S. Barriers to access include stigmatization of mental illness among different cultural groups and limited financial resources. Health care disparities can occur also as a function of age, geographic location, socioeconomic status, and other factors. Research on health behaviors related to AIDS is also increasingly important, particularly to minorities; African American women are experiencing a disproportionate increase in HIV infection rates. The following are highlights of NIMH-funded research addressing AIDS and health disparities.

Intervention Reduces HIV Transmission and STDs among HIV-infected Women

HIV transmission prevention strategies that focus on HIV-positive women may be key in controlling the spread of the disease. Given such need, researchers led by Drs. Gina Wingood and Ralph DiClemente at Emory University created the WiLLOW (Women Involved in Life Learning from Other Women) intervention, which emphasizes gender pride, communication, safer sex skills, and healthy sexual and social relationships. In a randomized, controlled trial of 366 women living with HIV, researchers evaluated the efficacy of WiLLOW in reducing HIV transmission risk behaviors and the occurrence of sexually transmitted diseases (STDs), as well as in enhancing HIV-preventive psychosocial and social support factors. Over the 12-month followup, women in the WiLLOW intervention, relative to the comparison group, reported positive results, including fewer episodes of unprotected intercourse, lower incidence of bacterial STDs, greater HIV knowledge, greater condom-using skills, larger social support networks, and fewer partner-related barriers to condom use. This is the first trial to demonstrate that tailoring HIV transmission prevention strategies to the specific psychosocial needs of HIV-positive women can lead to reductions in risky sexual behavior and incident bacterial STDs. (Wingood, G.M., et al. *Journal of Acquired Immune Deficiency Syndromes* 37:S58-S67, 2004)

Skill-based Interventions Reduces Risky Behavior among Teenage Minority Girls

The number of sexually transmitted HIV infections among adolescent girls is increasing, especially among African Americans and Latinas. To determine the efficacy of a skill-based HIV/STD risk-reduction intervention in reducing self-reported unprotected sexual intercourse among these populations, Dr. John Jemmott 3rd and colleagues at the University of Pennsylvania conducted a randomized controlled trial with three-, six-, and 12-month followups. A total of 682 African American and Latino adolescent girls (average age of 15.5 years) were recruited from the adolescent medicine clinic of a children's hospital serving a low-income, inner-city community. The participants received one of three interventions based on cognitive-behavioral theory: an information-based HIV/STD intervention that provided information necessary to practice safer sex; a skill-based HIV/STD intervention that provided information and taught skills necessary to practice safer sex; or a health-promotion control intervention concerned with health issues unrelated to sexual behavior. Each intervention lasted a little more than four hours (250 minutes). After 12 months, the skills-intervention participants reported fewer sexual partners and were less likely to test positive for an STD (10.5 percent vs. 18.2 percent) than health-promotion control intervention participants. (Jemmott, J.B. 3rd et al., *Archives of Pediatrics and Adolescent Medicine* 159:440-449, 2005)

Partner Involvement in HIV Interventions Helps Curb Transmission Risk Behavior

There are 27 million people living with HIV in sub-Saharan Africa, with women comprising nearly 57 percent of these cases. In countries such as Zambia, infection rates may be as high as 25 percent. The majority of HIV infection occurs from sexual transmission in marital or cohabiting relationships. Dr. Deborah Jones and colleagues at Barry University in Florida adapted the Stress Management and Relaxation Training/Expressive Supportive Therapy, a cognitive-behavioral group intervention, from an urban U.S. context for urban Zambia. Their study assessed the influence of male partner participation on sexual risk behavior among HIV-positive Zambian women. The study's 180 female participants attended either one or four group intervention sessions, received sexual behavior skill training, and were encouraged but not required to bring their male partners. The 152 male participants were randomly assigned to high- or low-intensity (greater or lesser levels of participation in the intervention) group intervention sessions. Sexual risk behavior, strategies, attitudes, and knowledge were assessed at baseline, and six and 12 months. After the intervention, female participants whose partners had greater participation in the intervention reported higher rates of condom use, more positive condom attitudes, safer sex intentions, and less alcohol use. These findings highlight the influence of male partners in implementing effective risk

reduction interventions. (Jones, D.L., et al. *Journal of Urban Health* 82:iv92-iv100, 2005)

Cost-effectiveness of a Primary Care Treatment Program for Depression in Low-income Women in Santiago, Chile

Dr. Araya and colleagues compared the incremental cost-effectiveness of a stepped-care, multicomponent program with usual care for the treatment of depressed women in primary care in Santiago, Chile. A cost-effectiveness study was conducted on a previous randomized, controlled trial involving 240 women with DSM-IV major depression who were selected from a consecutive sample of adult women attending primary care clinics. The patients were randomly assigned to usual care or a multicomponent stepped-care program led by a non-medical health care worker. Depression-free days and health care costs derived from local sources were assessed after three and six months. A health service perspective was used in the economic analysis. Complete data were determined for 80 percent of the randomly assigned patients. After adjusting for initial severity of depression, women receiving the stepped-care program had a mean of 50 additional depression-free days over six months relative to patients assigned to usual care. The stepped-care program was marginally more expensive than usual care (an extra 216 Chilean pesos per depression-free day). There was a 90 percent probability that the incremental cost of obtaining an extra depression-free day with the intervention would not exceed 300 pesos ($1.04 U.S.). The stepped-care program was significantly more effective and marginally more expensive than usual care for the treatment of depressed women in primary care. Small investments to improve depression appear to yield larger gains in poorer environments. Simple and inexpensive treatment programs tested in developing countries might provide good study models for developed countries. (Araya, R., et al. *American Journal of Psychiatry* 163:1379-1387, 2006)

Differences in Male and Female Prevalence of Mental Disorders and Utilization of Mental Health Services in Two American Indian Reservation Populations

The American Indian Service Utilization, Psychiatric Epidemiology, Risk and Protective Factors Project (AI-SUPERPFP) provided estimates of the prevalence of mental disorders and utilization of services for help with those disorders in American Indian populations. A total of 3,084 tribal members (1,446 in a Southwest tribe and 1,638 in a Northern Plains tribe) between the ages of 15 and 54 years and living on or near their home reservations were interviewed using an adaptation of the University of Michigan Composite International Diagnostic Interview. The most common lifetime diagnoses in the American Indian populations were alcohol dependence, posttraumatic stress disorder (PTSD), and major depressive episode. Compared with National Comorbidity Study (NCS) results, lifetime PTSD rates were higher in all American Indian samples. Lifetime alcohol dependence rates were higher for all but Southwest women, and lifetime major depressive episode rates were lower for Northern Plains men and women. After accounting for differences in demographic variables, both American Indian samples were at heightened risk for PTSD and alcohol dependence but at lower risk for major depressive episode when compared with the NCS sample. American Indian men were more likely than those in the NCS to seek help for substance use problems from specialty providers; American Indian women were less likely to talk to nonspecialty providers about emotional problems. Help seeking from traditional healers was common in both American Indian populations and was especially common in the Southwest. The results suggest that these American Indian populations had comparable, and in some cases greater, mental health service needs when compared with the general population of the U.S. (Beals, J., et al. *American Journal of Psychiatry* 162:1723-1732, 2005)

Cost-effectiveness of Evidence-based Pharmacotherapy or Cognitive Behavioral Therapy Compared with Community Referral for Major Depression in Predominantly Low-income Minority Women

Researchers evaluated the intervention and health care costs, depression-free days, and quality-adjusted life years in 267 low-income women who participated in a treatment trial of major depression. Compared with the group of women who received community referral, women who received medication had significantly lower depression scores from month three to month 10. The group of women who received cognitive behavioral therapy also had significantly lower depression scores compared to that receiving community referral from month five to month 10. Both groups had more depression-free days than the community referral group. The cost per additional depression-free day was $24.65 for the medication group and $27.04 for the CBT group. While the costs were greater than community referral, the investigators concluded that both interventions were cost-effective. (Revicki, D.A., et al. *Archives of General Psychiatry* 62:868-875, 2005)

Initiatives

Request for Applications (RFAs)

- **Research on Interventions on Anorexia Building Interdisciplinary Careers in Women's Health**
  Co-sponsored with the ORWH
  (RFA-OD-06-004)
- **Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health**
  Co-sponsored with the ORWH
  (RFA-OD-06-003)

Program Announcements (PAs)

- **Mental Health Consequences of Violence and Trauma**
  (PA-04-075)
- **Women's Mental Health and Sex/Gender Differences Research**
  (PA-06-334)
- **Women's Mental Health in Pregnancy and the Postpartum Period**
  (PA-06-377)
- **Neurodevelopment and Neuroendocrine Signaling in Adolescence: Relevance to Mental Health**
  (PA-06-428)
- **Neurodevelopment and Neuroendocrine Signaling in Adolescence: Relevance to Mental Health**
  (PA-05-162)
- **Women's Mental Health in Pregnancy and the Postpartum Period**
  (PA-06-376)
- **Women's Mental Health and Sex/Gender Differences Research**
  (PA-06-333)
- **Translational Research on Eating Disorders**
  (PA-06-523)
- **Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers**
  Co-sponsored with the ORWH
  (PA-04-126)

Conferences and Workshops

- **Early Recognition of Eating Disorders in Children and Adolescents**
  The NIMH convened this workshop in January 2006 to identify approaches and opportunities applicable to research in the early recognition of eating disorders in the pediatric population. Experts in eating disorder research discussed critical topics associated with assessment and neurobiology of child and adolescent eating disorders. Representatives from the NICHD, the NIDDK, and the FDA attended the meeting to discuss research priorities for eating disorders in children and adolescents.
- **New Interventions for Menopausal Symptoms**
  The NIMH co-sponsored a meeting with the NIA and the ORWH in July 2006 on managing menopause symptoms as a followup to the State of the Science Conference on the Management of Menopause-Related Symptoms. Experts presented data on a number of topics, including perimenopause-related depression. There was an

examination of interventions for symptoms during the perimenopause. A followup meeting is planned for FY 2007.

- **NIMH Eating Disorders Classifications and Diagnostics Meeting**
  This June 2006 meeting focused on key topics of eating disorders classification research, including empirical approaches to classification, cultural and developmental issues, epidemiology, and other topics. It served as an initial platform to address issues relevant to the upcoming DSM-V.
- **NIH Seminar on Sexually Transmitted Diseases**
  NIMH staff co-organized with the ORWH a seminar on sexually transmitted diseases in March 2006. Topics included gender differences in sexually transmitted diseases, topical microbicides, prevention of sexually transmitted diseases in adolescent girls, and community perspectives on sexually transmitted diseases among adolescents and young women.
- **NIH Seminar on Women and Depression**
  The NIMH co-sponsored with the ORWH a seminar on women and depression in June 2005. Topics included postpartum depression in pediatric practices, depression during the menopause transition, cultural issues related to the diagnosis and treatment of women, and community perspectives on women and depression.

Health Disparities among Special Populations of Women

The NIMH encourages research on special populations of women who may experience health care disparities based on age, race, geographic location, sexual preference, socioeconomic status, physical disabilities, and other factors. Research involving women from these diverse groups is encouraged in the program announcements titled Sex Differences and Women's Mental Health, Women's Mental Health in Pregnancy and the Postpartum Period, and Mental Health Consequences of Trauma. In addition to these program announcements, the NIMH encourages research in special populations of both men and women through the following:

- **Community Participation in Research** (PAR-06-247)
- **Research on Rural Mental Health and Drug Abuse Disorders** (PA-06-478)
- **Research on Psychopathology in Intellectual Disabilities (Mental Retardation)** (PA-06-431)
- **Clinical Research on Mental Illness in Older Adults** (PA-06-422)

Highlights of individual research projects on special populations of women can be found in the section on Accomplishments above. Finally, the NIMH supports a conference grant on Rural Women's Health through the Pennsylvania State College of Medicine.

Gender Analysis

The NIMH encourages research through two program announcements on sex/gender research that are referenced above. These announcements encourage sex differences research across a broad array of scientific topics, from basic science to clinical trials and services research. In addition, investigators of Phase III trials are expected to perform separate sex/gender analysis at the completion of their studies. Recently completed large studies funded by the NIMH, such as the National Comorbidity Replications Study, the Clinical Antipsychotic Trials of Interventions Effectiveness, the Sequenced Treatment Alternatives to Relieve Depression, and the Systematic Treatment Enhancement Program for Bipolar Disorder, have all performed separate gender analysis. Highlights of individual studies focused on sex differences are discussed above in the Accomplishments section.

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, every

segment of society, and 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, epilepsy, and Rett syndrome. The NINDS supports basic, translational, and clinical research on these and other neurological disorders. While research on women's health is found across the NINDS portfolio, the Institute designates one staff member from the Division of Extramural Research as its representative to the NIH 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 (MS) is a chronic autoimmune disease of the central nervous system that causes inflammation and the loss of myelin, a protective covering around 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 impairment. Several disease courses are possible. About 10 percent of patients experience a primary progressive form of MS, where the disease worsens continuously. The relapsing-remitting type of MS, where episodes of worsening neurological function alternate with periods of partial or complete recovery, affects 85 percent of patients. Hormonal factors may influence MS; some forms of MS are about two-fold more frequent in women, and fewer relapses are reported during pregnancy. The NINDS supports research on the mechanisms of MS and other autoimmune disorders, as well as clinical and translational studies aimed at developing new therapeutic approaches to MS.

Chronic pain results from pain signals that keep firing in the nervous system for weeks, months, or even years. Some chronic pain conditions, such as migraine headaches or fibromyalgia, tend to be diagnosed more often in women than 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, mechanisms of pain processing, modulation, and regulation, and pain management.

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 U.S. and a major cause of disability in both women and men. In general, women have a lower risk of stroke than men. However, 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 to 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.

Epilepsy is characterized by chronic, recurring seizures caused by abnormal electrical activity in the brain. While antiepileptic drugs (AEDs), brain stimulation, or surgery can help many patients control the disorder, for others, 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. The NINDS supports a broad portfolio of basic, translational, and clinical studies of epilepsy and epileptogenesis. In addition, the NINDS funds the Anticonvulsant Screening Program (ASP), a drug discovery program focused on epilepsy and other closely related neurological disorders.

Rett syndrome is a childhood neurological impairment seen almost exclusively in females. Rett syndrome is characterized by severe cognitive impairment, autistic behavior, stereotypic movements, and frequently seizures. The disease is associated with mutations in a gene called MECP2, located on the X chromosome, that lead to an insufficient amount or abnormal function of the MECP2

protein. The NINDS supports research aimed at understanding the mechanisms of action of the MECP2 protein and at developing new potential therapies.

Accomplishments

Multiple Sclerosis (MS)

Women with MS Are Less Likely Than Men with MS to Have Children Who Develop MS

A combination of genes and unknown environmental factors works together to cause MS. MS is approximately twice as common among women as men. If men have greater physiologic resistance to MS, they might theoretically require stronger genetic predisposition than women to overcome this resistance. In this circumstance, men would be expected to be more likely to have children with MS. A recent NINDS-funded study of families with a parent and a child with MS showed that men with MS are 2.2 times more likely than women with MS to have a child who develops MS. The findings provide an insight into the transmission of MS, although they should not change how men with MS are counseled about the risk to their offspring. (Kantarci, O.H., et al. *Neurology* 67:305-310, 2006)

Sex Differences in the Activity of Immune Cells in the Brain

MS requires the presence of immune T cells in the nervous system. The T cells then activate microglia, specialized brain cells that mediate the immune response within the brain and are activated in MS. An NINDS-funded study examined sex differences in this mechanism. Results showed that T cells from female mice can cause a response in microglia, but those from male mice do not have the same effect. This sex difference may partially explain why MS is more frequent in women. (Dasgupta, S., et al. *Journal of Biological Chemistry* 280:32609-32617, 2005)

Sex Differences in a Genetic Risk Factor

Interferons are produced by immune cells to help fight infections and tumors. The expression of one type of interferon, called interferon gamma, varies by gender. An NINDS-funded study of MS patients in three countries showed that variations in the interferon gamma gene were associated with different levels of susceptibility to MS in men. Naturally occurring variations in the interferon gamma gene may contribute to the differences in susceptibility to MS between men and women. (Kantarci, O.H., et al. *Genes and Immunology* 6:153-161, 2005)

Sex Does Not Affect Long-term Prognosis

An NINDS-funded team sought to analyze prior studies to identify clinical and demographic factors associated with a poor long-term prognosis in relapsing-remitting MS, the main form of MS. Although men are commonly thought to have a worse MS prognosis, a rigorous study did not support this conclusion. Instead, a poor recovery from the first attack, a short interval between the first and second attacks, the early accumulation of disabilities, and bladder and bowel dysfunction at the onset of the disease predict a worse disease course. (Langer-Gould, A., et al. *Archives of Neurology* 63:1686-1691, 2006)

Pain

Sex Differences in Response to Morphine and Experimental Pain

Women often have a stronger response to experimental pain than men, but several studies have shown that women use less morphine after surgery. An NINDS-funded project examined whether morphine is more effective at suppressing pain in women than in men. No sex differences were found in the ability of morphine to inhibit experimental pain (e.g., heat, pressure or arm cuff pain). Interestingly, in men, morphine attenuated the cardiovascular response to the pain caused by a tight arm cuff; this was not seen in women. Women reported significantly more drug-related adverse effects to morphine than men. The lack of sex differences in the effectiveness of morphine contrasts with prior clinical and suggests that sex differences in responses to morphine might depend on the pain model and/or drug dose, as well as the specific end point assessed. (Filigim, R.B., et al. *Journal of Pain* 6:116-124, 2005)

Childhood Abuse History and Pain Perception

Many patients with chronic pain report a history of childhood physical and/or sexual abuse. A recent NINDS-funded study examined whether healthy young adults with a history of abuse were more sensitive to pain, which would increase their risk of developing clinical pain. In this experimental context, participants with a history of abuse were less sensitive to pain than participants with no abuse history. The effect was stronger for women. In addition, a history of abuse was correlated with increased pain complaints, poorer self-reported health, and more negative emotional reactions. These findings suggest a complex relationship between abuse history and pain. (Filigim, R.B. and Edwards, R.R. *Clinical Journal of Pain* 21:387-397, 2005)

Stroke

Genetic Risk Factors for Stroke in Young Women

The Stroke Prevention in Young Women Study is a large clinical study designed to identify genetic and environmental risk factors for ischemic stroke in women between the ages of 15 and 50. It has already led to the identification of several risk factors for strokes in young women. Certain variations in the gene for nitric oxide syntheses 3 (NOS3) may be associated with increased ischemic stroke susceptibility among young African American women. This gene normally makes a protein, which exerts a variety of protective effects on blood vessels. Variations in a second gene, called phosphodiesterase 4D (PDE4D), may also increase stroke risk for young women. This risk is magnified in African American women who also smoke cigarettes. The study is the first to identify a possible interaction between the PDE4D gene and an environmental factor in triggering stroke. These results help to show how specific genes contribute to stroke risk and may lead to new ways of preventing stroke. (Howard, G., et al. Stroke 36:1848-1851, 2005; Song, O., et al. *Human Molecular Genetics* 15:2468-2478, 2006)

Preeclampsia Increases Risk of Stroke over Lifetime

Stroke in pregnancy is associated with several factors including preeclampsia, a serious complication of pregnancy marked by high blood pressure, weight gain, and protein in the urine. An analysis of the data from the Stroke Prevention in Young Women Study showed that, over their lifetime, women with a history of preeclampsia are 60 percent more likely to have a non-pregnancy related stroke. A history of preeclampsia should, therefore, be considered a risk factor for stroke. (Brown, D.W., et al. *Stroke* 37:1055-1059, 2006)

Women Respond Better to tPA: A Mechanism

Previous reports suggest that women achieve a better outcome than men after intravenous thrombolysis for ischemic stroke, such as treatment with tissue plasminogen activator (tPA). One NINDS-funded study investigated whether sex differences in blood characteristics, such as coagulation, could explain this result. The findings show that, after treatment with intravenous tPA, blood was more likely to start flowing in the previously blocked vessels of female patients. This suggests that sex may need to be considered when deciding on the best therapeutic approach to stroke. (Savitz, S.I., et al. *Stroke* 36:1447-1451, 2005)

Epilepsy

One Type of Menopausal Hormone Therapy Can Increase Seizures

Previous reports have suggested that menopausal hormone therapy could increase seizure activity in postmenopausal women with epilepsy. A randomized, double-blind, placebo-controlled trial examined the effects of hormone therapy consisting of a combination of natural estrogens and synthetic progesterone. The study showed that this type of menopausal hormone therapy was associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. Part of these results may be due to the synthetic form of progesterone used, as natural progesterone has been shown to be beneficial in some epilepsy patient. (Harden, C.L., et al. *Epilepsia* 47:1447-1451, 2006)

Valproate Increases Risk of Birth Defects

A recent NINDS-funded study examined the occurrence of birth defects and fetal death with four common epilepsy drugs: valproate, phenytoin, carbamazepine, and lamotrigine. Valproate posed the highest risk to the fetus, with more than 20 percent of the pregnancies exposed to valproate resulting in death or birth defects, such as skull and limb deformities and brain, heart, and lung problems. The study findings are consistent with several other recent studies and suggest that women with epilepsy should avoid using valproate during pregnancy. (Meador, K.J., et al. *Neurology* 67:407-412, 2006)

A Possible Mechanism Linking Seizures and the Menstrual Cycle

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. NINDS-funded investigators examined whether neuronal excitability might change with the menstrual cycle and affect the risk of seizure. The results showed that the composition of certain brain inhibitory receptors varies with the estrous cycle in mice and cause changes in neuronal excitability, which could explain the occurrence of catamenial seizures. These results may lead to a better understanding of the link between hormonal changes and seizure frequency. (Maguire, J.L., et al. *Nature Neuroscience* 8:797-804, 2005)

Rett Syndrome

Deficits in Social Behavior and Learning in a Mouse Model of Rett Syndrome

Patients with Rett syndrome exhibit severe cognitive impairment, autistic behavior, and stereotypic movements. NINDS-funded studies used a mouse model of Rett syndrome to examine these features. One study showed that mice with a mutation in MECP2, the gene that causes Rett syndrome, exhibit deficits in social behavior, even before the appearance of any motor deficits. A separate study demonstrated that these mice also have learning and memory deficits. Neuronal activity in mouse brain areas involved in learning was also altered. These studies suggest MECP2 regulates the expression and/or function of genes involved in social behavior and learning. The study of these mice will facilitate the identification of the molecular basis of the impairments in Rett syndrome and related disorders. (Moretti, P., et al. Human Molecular Genetics 14:205-220, 2005; Moretti, P., et al. *Journal of Neuroscience* 26:319-327, 2006)

MECP2 Causes Increased Expression of Stress Hormone in a Mouse Model

Patients with Rett syndrome exhibit many signs of anxiety. An NINDS-funded study used a mouse model of Rett syndrome to examine whether the anxiety was a consequence of the disease or an intrinsic aspect of the disorder due to the genetic mutation in MECP2. The mice carrying a mutation in MECP2 also showed behavioral signs of anxiety and produce high levels of stress hormones. In addition, the mutation in MECP2 led to the overexpression of the gene that produces corticotropin-releasing hormone, a stress hormone. An overabundance of stress hormones could be contributing to other aspects of the Rett phenotype, such as memory impairments. These findings suggest new therapeutic avenues for Rett syndrome. (McGill, B.E., et al. *Proceedings of the National Academy of Sciences of the United States of America* 103:18267-18272, 2006)

Initiatives

Request for Applications (RFAs)

- **Biomarkers for Neurodegeneration**
  This RFA solicited applications aimed at identifying biomarkers for neurodegenerative disorders, including Alzheimer's, Parkinson's, or Huntington's disease, stroke, and chronic pain. Markers that could help diagnose neurodegenerative conditions before symptoms appear would be tremendously valuable for developing more effective and earlier treatments across all areas of therapeutics research. (RFA-NS-07-004)

Program Announcements (PAs)

- **Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair**
  This PA with set-aside funds encourages preclinical and clinical studies to develop

new therapeutic approaches to MS, particularly neuroprotective and regenerative therapies. (PAS-06-266 and PAS-05-002)

- **Neurobiology of Persistent Pain Mediated by the Trigeminal Nerve**
  This PA 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 and PAS 06-199)
- **Biobehavioral Pain Research**
  This PA 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**
  This PA 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)
- **Neurovascular Mechanisms of Brain Function and Disease**
  This PA 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 and PAS-06-200)
- **Reducing Stroke Disparities Through Risk-factor Self-management**
  This PA solicits applications that will identify effective, culturally acceptable interventions involving self-management of risk factors for first and recurrent stroke for members of minority populations. (PAS-03-166)
- **Reducing Disparities in the Treatment of Epilepsy**
  This PA encourages research to identify effective interventions to overcome the key barriers to treatment for epilepsy experienced by minority groups and thereby improve the patterns of epilepsy care among these populations. (PAS-03-164)
- **Basic and Clinical Research on Rett Syndrome and MECP2**
  This PA invites a broad range of projects to investigate the neurobiological basis of Rett syndrome and develop potential therapeutic approaches. (PAS-05-024 and PAS-06-274)
- **Neuroprotective CNS Barriers in Neurological Diseases**
  This PA 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 the treatment of neurological diseases, including stroke, MS, and other disorders of special interest to women. (PAS-03-165)
- **Gene Discovery for Complex Neurological and Neurobehavioral Disorders**
  This PA aims to promote the identification of susceptibility genes for complex neurological and neurobehavioral disorders. These disorders are caused by the interaction of multiple genes or by a combination of genetic and environmental risk factors. Many of these disorders, such as stroke or epilepsy, are relatively common and affect women. (PAS-06-204, PAS-03-092)
- **Understanding and Treating Tuberous Sclerosis Complex**
  This PA is intended to stimulate research on the molecular, genetic, developmental, and pathophysiological aspects of tuberous sclerosis and on preclinical therapy development and clinical research. (PAS 06-205, PAS-06-206, and PAS 05-085)

Conferences and Workshops

- **Nonepileptic Seizures Treatment**
  In May 2005, the NINDS, the NIMH, and the American Epilepsy Society held a small,

international workshop on nonepileptic seizures (NES). NES is a neuropsychiatric disorder that presents with a combination of neurological signs, underlying psychological conflicts, and without associated epileptogenic pathology. Between 10 and 50 percent of patients with intractable epilepsy may have either pure NES or a combination of epileptic and nonepileptic seizures. Researchers and clinicians from many disciplines assessed the state of the science and developed specific research strategies that can be expanded to involve a large segment of the epilepsy and psychiatric treatment communities. The results of these preliminary discussions were presented at the annual American Epilepsy Society meeting and at meetings of the psychiatric and nursing societies for further discussion. The meeting report can be found at: http://www.ninds.nih.gov/news_and_events/proceedings/2005_nonepileptic_seizures.htm.

- **NINDS Workshop on Biomarkers of Epileptogenesis**
  In September 2006, the NINDS sponsored the Biomarkers of Epileptogenesis Workshop to explore potential methods of identifying those individuals who are at higher risk of developing epilepsy after a neurological injury, such as stroke, traumatic brain injury, or febrile seizures. Basic and clinical epilepsy researchers, as well as experts in other fields pursuing biomarker development, discussed a number of candidate technologies that might provide reliable biomarkers to predict the risk of developing epilepsy. These technologies include genomics, proteomics, imaging, and electrophysiology, some of which are being incorporated into ongoing trials of epilepsy prevention therapy.
- **NIH Pain Consortium Symposium: Highlights in Pain Research 2006**
  In April 2006, the NINDS and the other NIH Institutes participating in the Pain Consortium sponsored a symposium to highlight recent advances in pain research. The topics included genetics and pain, cellular mechanisms of pain, imaging in pain, cognitive and emotional aspects of pain, and novel therapies. The symposium aimed to foster new ideas, as well as highlight the work of new investigators. The full meeting agenda can be found at: http://conferences.masimax.com/painconsortium/agenda.cfm.

Health Disparities among Special Populations of Women

See previous Initiatives section for the NINDS activities related to health disparities in women.

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 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 sex 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 mission of the National Institute of Nursing Research (NINR) is to support clinical and basic research that establishes a scientific basis for the care of individuals across the life span. NINR-supported research encompasses the health of individuals, their families, and their caregivers. It also focuses on the special needs of at-risk and underserved populations, with an emphasis on health disparities. The Institute's research focus transcends many disciplines to promote health and improve patient and caregiver quality of life across a broad range of diseases and conditions. The NINR unites the disciplines of biological and behavioral sciences to elucidate the complex interactions between the physiological factors of health and disease and the behavior, decisions, and perceptions of the individual. Taken together, the elements of the NINR's mission

shape a forward-looking research agenda whose relevance is underscored by today's health care challenges and opportunities.

In 2006, the NINR released its new five-year strategic plan, titled Changing Practice, Changing Lives. Developed in close consultation with representatives of the extramural community, this new plan details the NINR's scientific priorities. The Institute will focus its research on health promotion and disease prevention; improving quality of life through self-management, symptom management, and caregiving; eliminating health disparities; and leading critical research on the end of life. The plan also highlights four cross-cutting strategies for advancing nursing science, including: advancing the integration of biological and behavioral sciences; promoting the design and use of new patient care technologies; improving nursing science methods; and developing the next generation of investigators. The full text of the strategic plan elaborates on each of these areas and can be found on the NINR's Web site at www.ninr.nih.gov.

The NINR's mission and research goals are inherently suited to addressing the current challenges in women's health research. NINR-supported investigators have made numerous key findings during FY 2005 and 2006, further advancing our understanding of the many issues uniquely relevant to women. These areas include improving maternal and perinatal health, aging, cardiovascular health, pain management, and HIV/AIDS prevention and treatment. The NINR also sponsors or co-sponsors a number of research initiatives on topics related to women's health, including pain research, chronic fatigue syndrome, improving care for dying children, and increasing the participation of women in clinical trials.

The elimination of health disparities is a critical cross-cutting area of research throughout the field of women's health, and this is certainly true at the NINR. Consistent with its strategic goal of supporting research into the causes of health disparities and finding ways to overcome them, the NINR maintains a robust research portfolio that studies the disparities experienced by women in minority, rural, and other underserved populations. In FY 2005 and 2006, NINR investigators made strong gains in these areas, including designing ways to improve social support among chronically ill women in rural areas, promoting mammography screening among black women, developing a mental health intervention to decrease depression among single mothers, and improving knowledge of HIV prevention among Latinas.

The NINR is committed to improving clinical practice through the generation of new knowledge and the development of leaders in nursing science. Today's challenges in the field of women's health present unprecedented opportunities for the Institute to further expand its impact on the health of the nation. By focusing on the areas of research outlined in its strategic plan, areas which are aligned with critical public health needs, the NINR will ensure that these challenges are proactively addressed.

Accomplishments

Maternal/Perinatal Health

Health issues surrounding pregnancy and the perinatal period comprise a significant part of the NINR's overall research portfolio in women's health. NINR investigators continue to make important progress in these critical areas of science, in a continuing effort to improve pregnancy outcomes and ensure the health of both mother and child. One recent study, which received significant coverage in the national media, found that a child's weight may be influenced by its mother's weight even before the child is born. Researchers analyzed data for more than 3,000 children included in the National Longitudinal Survey of Youth's Child-Mother file. They found that a child is more likely to be overweight at a very young age—at two or three years old—if the mother was overweight or obese before she became pregnant. A mother's weight within one to two months before she became pregnant had the greatest impact on a child's weight. If a woman was overweight before she became pregnant, her child was nearly three times more likely to be overweight by age seven compared with a child whose mother was not overweight or obese. The risk that a child would be overweight at a young age increased with the degree of the mother's obesity. The data also indicate that other prenatal characteristics, particularly race, ethnicity, and maternal smoking during pregnancy, place a child at

greater risk of becoming overweight. These results underscore the importance of prenatal care and the health habits of the mother before and during pregnancy since these may impact the health of the child through the early years of childhood and possibly adulthood.

Other NINR research focused on the process of childbirth itself. A significant proportion of pregnant women who deliver vaginally suffer some form of laceration or other trauma to the birth canal, which can cause pain, require suturing, and lead to long-term problems of bowel, urinary, or sexual function. Using data from more than 1,100 women who delivered vaginally under the care of a midwife, researchers examined factors related to the experience of childbirth trauma. Three-quarters of the women experienced some form of trauma during childbirth, while one-fifth received a laceration large enough to require suturing. The risk of trauma was highest for white women as well as for women experiencing their first delivery, women who delivered larger babies, or women over 30 years of age. Also, women who did Valsalva pushing (holding the breath and actively pushing during a contraction) had more trauma while women who delivered the head between contractions had less trauma. These findings indicate that older pregnant women and first-time mothers may need special attention and that childbirth techniques emphasizing delivery in a controlled and unrushed manner without pushing may reduce trauma associated with normal, spontaneous vaginal births.

Current practice during the birth of a preterm infant calls for clamping the umbilical cord immediately after delivery, which may prevent adequate transfer of blood from the placenta into the circulation of the infant. Scientists compared the immediate effects and the long-term health outcomes of immediate versus delayed cord clamping for infants born before 32 weeks gestation. The average time to cord clamping was seven seconds in the immediate group, and 32 seconds in the delayed group. There were no differences noted between the groups in terms of initial blood pressure or temperature, long-term oxygen or ventilator use, long-term lung damage, number of blood transfusions required, or overall survival. However, infants in the delayed group had a lower rate of late-onset sepsis (LOS), which carries a high risk of morbidity and mortality, and of intraventricular hemorrhage (IVH), which carries a risk of developmental or neurological deficits. This effect was stronger in male infants than in females. These findings indicate that delaying the cord clamping at delivery for infants born at less than 32 weeks gestation may offer protective benefits from both LOS and IVH, common complications of prematurity.

Pregnant women with complications from diabetes, high blood pressure, or other conditions are at high risk for delivering their infant preterm or with low birth weight. Investigators tested a prenatal care intervention delivered by specially trained advanced practice nurses (APNs) to a group of high-risk pregnant women. The program was delivered by a team of APNs, who provided in-home prenatal visits that replaced half of the usual prenatal physician or clinic visits. Researchers conducted a secondary analysis of the logs kept by the APNs and examined the frequency and nature of collaborative contacts between the APNs and the women's physicians. These contacts were most often initiated by the APNs to provide status updates or to discuss such things as lab results, treatment adherence, or need for further testing. Investigators found that the APNs delivering the prenatal care were capable of assessing high-risk patients, negotiating the health and social systems, and working collaboratively with physicians. The research team concluded that the intervention helped more of these high-risk women carry their infants to term, resulting in a decrease of total hospital days and a significant savings of medical costs over the infant's first year of life.

Women and Aging

The NINR maintains a diverse research portfolio on the multiple health issues surrounding women and aging, including issues associated with menopause. For example, the NINR is a co-sponsor of the multisite Study of Women's Health Across the Nation (SWAN) with the National Institute on Aging (NIA). The SWAN examines women between 40 and 60 years old—the period of the menopausal transition where scientific data have historically been limited. After menopause, studies have shown that women often have a slow but steady loss

of bone mineral density (BMD). SWAN investigators followed more than 2,300 middle-aged women over a four year period to measure changes in BMD, along with fluctuations in follicle-stimulating hormone (FSH), estradiol (a metabolite of estrogen), and several forms of androgens. The study found that the women experienced a steady decline in BMD over the four year study period. In the lumbar spine, BMD decreased by 3.2 percent for women in perimenopause, 3.9 percent for women in menopause due to surgical removal of their ovaries, and 5.6 percent for women in natural menopause. At baseline, higher FSH levels corresponded with lower BMD, and there was a complex interaction of FSH levels and BMD over the study period. However, BMD loss was not related to estradiol until the level of this hormone dropped below a threshold value. No relationship was found between BMD and androgen levels. These findings indicate that FSH may play a direct role in maintaining bone mass, and serial FSH measurements may help predict BMD loss in menopausal women.

Decreases in activity and muscle strength, often related to pain and the development of osteoarthritis, may start in middle age and begin a process leading to functional disability later in life. Researchers assessed the walking and stair-climbing ability of almost 900 pre- or perimenopausal women, including a cohort from the SWAN. Approximately 30 percent reported knee pain, and 20 percent had evidence of knee osteoarthritis. On a flat, carpeted surface, one-third of the women walked slower than the federal standard walking speed for crossing a street, with 12 percent walking slow enough to indicate frailty. Women who were older, had more body fat, and/or reported knee pain tended to have slower walking gaits. Slower time going up and down a set of stairs was related most closely to the presence of knee osteoarthritis and pain, low skeletal muscle mass, and poor quadriceps muscle strength. There were no significant differences in performance noted by race. These findings indicate that one-third of middle-aged women may be at risk for disability as indicated by their normal walking gait speed, and these women may benefit from interventions to forestall any further functional decline.

Increasing attention has been focused in recent years on the effects of the sex hormones, especially estrogen and testosterone, and their relationship to carbohydrate and lipid metabolism, cardiovascular disease, or diabetes. The genes of four proteins involved in estrogen synthesis and action have been identified, including: CYP 19, an enzyme which converts androgens into estrogens; 17HSD, an enzyme which helps make estradiol; and the cellular estrogen receptors ER alpha and ER beta. Researchers evaluated the genotypes of 1,538 participants who were enrolled in the SWAN genetics subgroup for variations in the genes encoding these four proteins and their relationship to the incidence of metabolic syndrome (a precursor to diabetes), insulin resistance, and diabetes. Analysis of single nucleotide polymorphisms (SNPs or single-base variations) of the four genes found that: (1) certain SNPs of CYP 19 were associated with diabetes and insulin resistance in white, black, and Japanese women; (2) three SNPs of 17HSD were highly related to diabetes in white women but not in other ethnic groups; (3) selected SNPs of ER alpha were associated with insulin sensitivity in Japanese and Chinese women; and (4) selected SNPs of ER beta were associated with metabolic syndrome among Chinese and Japanese women. These findings indicate that certain genetic factors affecting sex hormone synthesis and function may be linked to insulin sensitivity and the development of metabolic syndrome or diabetes and that these factors can vary between ethnic groups.

More than one-quarter of women do not engage in any regular form of exercise, even though consistent, moderate activity has been shown to lower mortality rates. Researchers tested an exercise program with a group of sedentary, midlife women in which participants received an individualized walking program based on an initial health assessment and aerobic fitness test. The women kept an exercise diary and wore a heart rate monitor to measure exercise compliance. A member of the research team met with each participant every two weeks to review progress and provide support. This intervention phase lasted six months. To study exercise maintenance, the women were also asked to keep their exercise diaries for another six months. One-fifth of the women adhered consistently to their

exercise program, and 11 percent showed occasional lapses. However, most of the remaining women dropped out or lapsed to a less active pattern. Women with good adherence to exercise during and following the program had a higher estimate of their own ability to reach fitness goals, had better aerobic fitness, and showed a larger decrease in body fat than women who dropped out of the program. Women with good adherence stated that the encouragement and strategies they learned in the active intervention phase helped them maintain good exercise habits.

Cardiovascular Health in Women

The NINR supports a number of studies related to the cardiovascular health of women, including several that examine the prevention, early detection, and treatment of coronary heart disease (CHD) and related morbidities. The Framingham Risk Estimation (FRE), a diagnostic test often used to assess CHD risk, does not take into account family history of heart disease and thus may underestimate the risk for women from families with a history of CHD. For a group of asymptomatic women who were siblings of a person hospitalized with premature CHD, researchers compared FRE scores with measurements of their coronary artery calcium (CAC), which has been shown to indicate the presence and extent of calcified plaques within the coronary arteries. Almost all of the women in the study had FRE scores that classified them as low risk for CHD. However, 40 percent had detectable levels of CAC, with 6 percent showing severe and extensive coronary atherosclerosis. These findings indicate that adding an assessment of family history to the current screening procedures for women may help to identify those who are at risk for CHD at an earlier stage and may benefit from beginning early preventative measures, such as dietary changes, weight loss, low-dose aspirin, or lipid-lowering medications.

While cardiovascular disease (CVD) is the leading cause of death among women in the U.S., there remain significant differences among ethnic groups in disease rates and risk factors due to a complex mix of cultural, experiential, geographic, sociodemographic, and genetic attributes. Using data collected from more than 2,800 premenopausal women in the SWAN, NINR-supported researchers examined ethnic variations in CVD risk factors. Japanese and Chinese women had the lowest average body mass index (BMI) and black women the highest. Black women were also the most likely to be taking blood pressure medications and to be current smokers. Composite risk scores were calculated from several risk factors, including blood pressure, BMI and waist circumference, smoking status, and serum levels of lipids, glucose, insulin, clotting components, and inflammation markers. Black and Hispanic women had the highest composite risk scores, and Japanese and Chinese women had the lowest. The results suggest that interventions to lower CVD risks should take into account ethnic differences in disease prevalence and risk.

Previous NINR-supported research concluded that women suffering a heart attack exhibit different symptoms than those experienced by men and that women often delay seeking treatment when experiencing the symptoms of a heart attack. These findings raise many concerns because rapid treatment of a heart attack can greatly reduce the risk of death and disability. In a recent study, interviews with women who had recently suffered a heart attack revealed two treatment decision trajectories following the onset of symptoms, which researchers described as "knowing" and "managing." Women in the knowing group understood that their symptoms were serious and knew they would need help, even if they did not believe they were experiencing a heart attack. Some of the women in this group sought treatment immediately, but others waited for a convenient time go to the hospital or delayed until a family member or co-worker insisted on calling for help. Women in the managing group tried to manage or ignore their symptoms before seeking help. Improved knowledge of such decision trajectories could help clinicians to design better educational interventions to improve the awareness of cardiac symptoms among women and highlight the importance of seeking early entry into treatment.

In the first year following a heart attack, women have both greater morbidity and mortality and show poorer psychological adaptation than men. Researchers interviewed recent heart attack sufferers and found that

women were less likely than men to make changes to their diet or exercise routines, changes that could prevent future heart attacks. A possible reason for this failure is that the women interviewed in the study were less likely to attribute the cause of their heart attack to poor diet and exercise than the men. These findings indicate that men and women differ in what they believe caused their illness, which may influence their behavior once they have recovered. Findings such as these can help health care providers develop tools to teach women how to recognize the symptoms of a heart attack, the importance of seeking rapid treatment, the causes of a heart attack, and the behavior changes necessary to prevent a reoccurrence.

In 2006, the NINR released a new publication, Subtle and Dangerous: Symptoms of Heart Disease in Women. This informational booklet, available both in hard copy and on NINR's Web site, provides lay readers with a comprehensive summary of NINR-sponsored research on women's experiences with heart disease. The booklet presents the results of studies related to: heart disease risks for women; the subtle symptoms of heart attacks in women; recovery and rehabilitation for women following a heart attack; women with chronic angina; and women with peripheral artery disease. It reminds readers of risk factors that they cannot control, namely family history and age, but it also lists risk factors that they can take action against, such as smoking, high blood pressure, and physical inactivity.

Pain Management in Women

As a member of the NIH Pain Consortium, the NINR maintains a diverse portfolio on pain research. The Institute supports projects that examine the causes and treatment of acute and chronic pain, many with a special emphasis on issues related to women and gender differences. In FY 2005 and 2006, NINR researchers continued to make progress in these areas. Previous NINR-supported studies have found that women often receive good relief of acute, short-term pain from nalbuphine, a kappa-opioid medication. In contrast, this medication may induce a heightened pain response in men. This finding indicates that nalbuphine has both analgesic and antianalgesic properties and that pain receptors may be gender-specific. One subtype of pain receptor, the sigma receptor, is thought to block the pain-relieving effects of opioids and thus may play a role in the antianalgesic effects of nalbuphine. Researchers administered different combinations of medications to patients after they had undergone oral surgery for an impacted molar. All patients received nalbuphine, while some received one of two neuroleptic medications (haloperidol or chlorpromazine), which are known to block sigma-receptors. Of patients who received nalbuphine alone, women received significantly greater pain relief than men, a result consistent with previous studies. Men who received nalbuphine with one of the neuroleptics reported greater pain relief than those who received nalbuphine alone, but there was no significant difference for women. These findings indicate that neuroleptics can block the antianalgesic properties of nalbuphine, which may lead to the development of new analgesics.

People with chronic non-malignant pain (CNMP) may develop depression, disability, and feelings of powerlessness from its long-term effects. Women are more likely to experience CNMP than men. In an effort to develop non-pharmacological methods to promote pain control, researchers tested two music-based interventions on a group of patients with CNMP, which included mostly women. In this study, two-thirds of the participants were given music tapes, either standard or patterned to their own tastes, and they were instructed to listen to their music at least one hour each day at a time of their choosing. The remaining third served as a control group and continued in their standard care. After one week, when compared with controls, participants in the music group reported decreases in pain, disability, and depression, and an increased sense of power over their pain. In addition, many patients in the music intervention reported that the music and pain diary helped them better manage and understand their pain. These results suggest that a non-pharmacological intervention, such as music, can help to alter patterns of pain perception, disability, control, and depression in persons experiencing CNMP.

Irritable bowel syndrome (IBS), a condition that predominately affects women, is charac-

terized by abdominal pain, a sense of bloating or distension, and a change in stool patterns involving either constipation or diarrhea. People with IBS generally report a poorer quality of life (QOL) compared with those without this condition. In a secondary analysis of data collected during three clinical trials, researchers analyzed the symptom diaries kept by more than 200 women with IBS. They found that the most frequently reported symptoms were intestinal gas and abdominal pain; the least common symptom was diarrhea. Participants reported no IBS symptoms on fewer than 10 percent of the diary days. The women rated intestinal gas as the worst symptom on half of the symptom days and abdominal pain on one-third. However, abdominal pain had the largest overall impact on decreased QOL. Although less frequent, diarrhea, when it occurred, also had a significant negative impact on QOL. These findings indicate that, for women with IBS, abdominal pain and diarrhea tended to have the greatest impact on QOL even though they were less frequent than feelings of bloating or gas.

HIV/AIDS Prevention and Treatment

As part of a comprehensive portfolio in the prevention and management of HIV/AIDS, the NINR supports a number of studies focused specifically on these topics as they relate to women. The Institute also supports other projects examining gender differences and HIV/AIDS. In one recent study, researchers tested the effectiveness of a culturally sensitive, educational intervention designed to reduce risk factors for HIV among Latinas. Urban-dwelling Latinas in the U.S. are at an elevated risk for HIV transmission, and more than half of those who are HIV positive acquired the infection through heterosexual contact. One significant risk factor is the cultural barrier that inhibits these women from discussing safe sex practices with their partners. NINR-supported scientists developed an intervention tailored to decrease risky sexual behaviors among low-income Latinas that involved educational sessions provided by bilingual HIV counselors and instructors. Six months after the program, women in the intervention group reported improved HIV knowledge and communication skills.

Many patients with HIV/AIDS report fatigue as a frequent and debilitating symptom that can decrease quality of life and lower their adherence to highly active antiretroviral treatment (HAART) regimens. Using data collected in a large study of HIV-infected patients, scientists explored the intensity of fatigue as influenced by demographic, cultural, and illness variables, and evaluated the contribution of fatigue to physical and mental health. This secondary analysis of data found that reports of fatigue intensity were highly variable, with 12 percent of those studied having no fatigue, 30 percent having mild fatigue, 31 percent moderate fatigue, and 27 percent severe fatigue. Black patients reported lower fatigue than whites or Latinos, and women had significantly higher fatigue scores than men. Individuals who reported low incomes and had high depression scores also had higher fatigue intensity. Symptom clusters, including fatigue, shortness of breath, lipodystrophy (an abnormal distribution of fat in the body), and depression, were the most significant contributors to perceptions of both physical and mental health. Overall, results indicated that blacks report a different pattern for fatigue than other groups, while women and those living in poverty tend to have higher fatigue levels.

Many people with HIV infection report sleep disturbances than can significantly affect their ability to function independently and to remain employed. A survey of the sleep quality among HIV-infected black women found that almost one-quarter of the women described their sleep quality as fair to very bad, and one-half reported less than seven hours of sleep per night. Roughly one-third reported at least occasional use of sleep medications. From a standard sleep scale, half were found to have significant sleep difficulties and were categorized as poor sleepers, with the remaining participants classified as good sleepers. Good sleepers scored significantly higher on both physical and mental quality of life scales than poor sleepers. Sleep quality contributed to differences in body pain, mental health, physical and social function, and vitality and was a more significant factor in quality of life than stage of illness. These results suggest the need for better interventions to improve sleep quality among HIV-

positive women, which could significantly improve quality of life for these patients.

Initiatives

Program Announcements (PAs)

- **Health Disparities among Minority and Underserved Women**
  The purpose of this initiative, sponsored by the NINR in collaboration with other NIH ICs as well as the NIH ORWH, is to stimulate research to reduce health disparities among racial/ethnic minority and underserved women. This initiative calls for research that improves our knowledge of factors influencing health promotion and risk reduction in these populations, including social, economic, cultural, and community factors. (PA-07-154, formerly PA-04-153)
- **Mechanisms, Models, Measurement, and Management in Pain Research**
  This initiative, sponsored by the NINR in collaboration with the other NIH ICs of the NIH Pain Consortium, seeks to stimulate a wide range of basic, clinical, and translational research studies on acute and chronic pain across all disciplines. This initiative includes biobehavioral, genetics, and pain management research. Women are particularly affected by several of the conditions of special interest in this initiative, such as osteoporotic pain, fibromyalgia, and TMJ and muscle disorders. (PA-06-542, PA-06-543, PA-06-544)
- **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 the bereavement following the death for the children's families, friends, and care providers. This research has implications for women, who are most frequently the caregivers of ill and dying children. (PA-04-057)
- **Chronic Fatigue Syndrome—Pathophysiology and Treatment**
  The NINR is a co-sponsor of this initiative, which is administered by the ORWH. The initiative seeks to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS) in diverse groups across the life span. Of particular relevance to the strategic goals of the NINR, the initiative calls for research on behavioral factors that influence CFS and on ways to manage symptoms and otherwise improve the quality of life of those affected by CFS. (PA-07-263, PA-07-264, PA-07-265, formerly PA-05-030)
- **Enrolling Women and Minorities in HIV/AIDS Research Trials**
  Women and minorities are frequently underrepresented in clinical trials, and there is a need to identify and correct barriers to participation by these groups. The NINR is a co-sponsor of this initiative. The goal is to support research that will identify factors negatively impacting the recruitment of women and minorities into HIV/AIDS clinical trials and to develop interventions that will facilitate the recruitment and retention of these populations. (PAS-03-168)
- **Reducing Preterm and Low Birth Weight in Minority Families**
  The NINR is a co-sponsor of this PA, which encourages collaborative, multidisciplinary, biobehavioral research on the mechanisms underlying disparities in pregnancy outcomes as well as interventions to reduce such disparities. Differences in pregnancy outcomes among minorities are largely due to preterm delivery and low both weight, which disproportionately affect these populations. (PA-04-027)

Health Disparities among Special Populations of Women

The NINR's new strategic plan, titled Changing Practice, Changing Lives, highlights the elimination of health disparities as an area of research emphasis that cuts across nearly all the Institute's research portfolio. The NINR grants related to women's health are no exception. Special populations of women encompassed by NINR health disparities research include women of racial and ethnic minorities, women of low socioeconomic status, and women who reside in rural areas. In addition to the research advances discussed in the following paragraphs, several of the findings

discussed in previous sections are also examples of NINR's recent accomplishments in the area of health disparities research.

For middle-aged women living in rural areas with few health care resources, a chronic illness can present many challenges in self-management and impose changes in physical and emotional well-being. Researchers in Montana evaluated the use and effectiveness of the Internet-based Women to Women (WTW) Project among rural-dwelling women living with a variety of chronic conditions, such as diabetes, arthritis, heart disease, or multiple sclerosis. The WTW Project provided the women with Internet access and a Web site that included an online chat room for use among the participants, e-mail access to other participants and the research team, health education activities, and a separate chat room facilitated by a health care expert specifically to discuss health information. Compared with women in a control group without access to the WTW Project, participants in the project showed a greater improvement in self-esteem, social support, and empowerment after three months. In addition, women in both groups showed declines in depression, stress, and loneliness. Use of computers and the Internet for access to health information is increasing among rural populations, and interventions, such as the WTW Project, could help lower social isolation and improve the psychosocial outcomes of rural women adapting to or managing a chronic illness.

Yearly mammography screening is the most effective method for the early detection of breast cancer in women over 40 years of age. Previous studies indicate that black women tend to be inconsistent in adhering to this yearly schedule, especially over longer time periods. Researchers followed more than 600 older black women for five years to assess their mammogram use and their attitudes and beliefs toward mammography. While 14 percent of the women received yearly mammograms over the study period, half received two or fewer. Overall, women with lower education or income had the fewest mammograms. Good knowledge of mammography guidelines and recommendations from health care providers improved screening compliance by two- to three-fold. Those who underwent yearly mammograms reported higher self-efficacy and fewer perceived barriers to the procedure than those with only one mammogram. Barriers to screening included inconvenience, embarrassment, time, pain, costs, and worry about finding cancer. These findings detail the types of concerns that researchers must take into account when designing interventions for increasing cancer screening habits among black women, indicating that such programs may need to address knowledge and beliefs about the procedure and find ways to decrease perceived barriers.

Single mothers, who often live in poverty, are at high risk for depression due to loneliness, lack of social support, low self-esteem, and the stresses of providing for their family. Maternal depression is an important concern because it can hinder the development and maturation of children in the family. In a randomized, controlled trial, researchers tested an intervention to address depressive symptoms among low-income single mothers who were assessed to be at high-risk for depression. In small group sessions, a psychiatric nurse led classes to help the mothers identify behaviors that fostered depression or distorted thinking and learn how to decrease or stop negative thoughts. Group treatment allowed for peer contact to reduce isolation and promote behavioral change. The mothers in both the intervention group and a non-intervention control group completed questionnaires on depressive symptoms and life stressors at four points over a one-year period. Mothers who participated in the intervention showed a steady decline in all areas of depression and stress. However, the researchers noted that even mothers in the control group showed some decline in symptoms and stressors over time; having a member of the research team listen to their problems and concerns may have decreased the sense of isolation. This simple and low-cost intervention can teach low-income single mothers techniques to improve their mental health by identifying and addressing their depressive symptoms.

Gender Analysis

An important component of many studies supported by the NINR is an examination of gender differences with respect to diseases or conditions or to the effectiveness or efficacy of

clinical interventions. In accordance with the NIH standing policy, all proposed NINR clinical studies are carefully screened for inclusion of both men and women, as appropriate. In addition, many NINR-supported clinical studies are specifically designed to analyze gender differences. For example, studies that test novel behavioral interventions can often compare the effectiveness of the intervention in women versus men. Several of the research advances discussed above make use of gender as a variable; the first advance, Pain Management in Women, is one such example. This study focused on the differing responses men and women had to certain analgesics and examined strategies for overcoming such differences. Also mentioned above, other NINR research has focused on different symptoms of a heart attack experienced by men and women. Consistent with the NINR's mission to provide a scientific basis of care for all people across the life span, the Institute's research is primarily clinical, and, therefore, analysis of gender differences will always play a critical role in NINR-supported research projects.

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 of Alzheimer's disease and other dementias, menopause and hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2005 and 2006, NIA-supported researchers made important progress in a number of women's health-related areas.

For example, ongoing research related to Alzheimer's disease is looking at the effects of menopausal hormone therapy on cognition. Mechanisms through which estrogen and related hormones work on the brain continue to be elucidated. Another recent study demonstrated that the elevated levels of follicle-stimulating hormone (FSH) seen in menopausal women may play a key role in bone loss and the development of osteoporosis. Research continues on the etiology and predictors of hot flashes in women around the time of menopause, as well as other symptoms that may accompany the menopausal transition, such as sleep problems and joint pain. NIA-supported investigators continue to explore the reasons behind gender differences in disability, morbidity, and mortality at older ages.

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 and ethnic backgrounds.
- **Women's Health Initiative Study of Cognitive Aging (WHISCA)**
  The WHISCA is an ancillary project of the Women's Health Initiative Memory Study (WHIMS) and the Women's Health Initiative (WHI), a randomized clinical trial of menopausal hormonal therapy. Since 1999, WHISCA has investigated the effects of menopausal hormonal therapy on longitudinal changes in memory and specific cognitive functions in older non-demented WHI participants.
- **Women's Health and Aging Study (WHAS)**
  WHAS I and II are major studies of the etiology of disability in older women. Although recruitment has ended, data analysis and reporting continue.

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 NIA also supported major workshops on women's health-related topics in FY 2005 and 2006. Of note was a state-of-the-science conference on the management of menopausal symptoms.

Older women outnumber older men in the U.S., and the proportion of the population that is female increases with age. In 2003, according to government statistics, women accounted for 58 percent of the population age 65 and over and for 69 percent of the population age 85 and older.# 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 (AD) and other types of dementia; menopause and hormone therapy; osteoporosis and hip fracture; physical disability; caregiver burden (research has shown that caregivers are more likely to be women); decline in function in older women; age-related muscle loss; and cancer in older women. The Institute has a Women's Health Coordinator in the Office of Planning, Analysis, and Evaluation who coordinates NIA activities related to women's health and serves as the liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and planned research initiatives aimed at women, are described in the following.

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 U.S. because of its enormous impact on individuals, families, the health care system, and society as a whole. Scientists estimate that as many as 4.5 million people currently suffer with this disease, and the number is expected to increase to 13.2 million by 2050, an almost three-fold increase. Currently, nearly half of all Americans ages 85 and older have AD (Hebert, L.E., et al. *Archives of Neurology* 60:1119-1122, 2003). 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. Moreover, the overall lifetime risk of developing AD for a woman is nearly twice that for a man (32 percent vs. 18 percent) (Hebert, L.E., et al. *American Journal of Epidemiology* 153:132-136, 2001).

Greater Vegetable Consumption Is Associated with Less Cognitive Decline with Age in Women

Previous epidemiological and laboratory studies have suggested that fruits and vegetables high in antioxidants may confer protection against cognitive decline with age. In a recent study of 13,388 older women who were followed over a 10- to 16-year period, investigators related fruit and vegetable consumption with subsequent cognitive performance. They found that women consuming the most green leafy vegetables experienced slower decline than women consuming the least amount of these vegetables. Consumption of fruits was not associated with cognition or cognitive decline. The investigators controlled for a wide array of possible confounding factors, including education, use of vitamin supplements, physical activity, alcohol intake, and smoking. Findings from this study strengthen the notion that a diet rich in vegetables may serve to maintain healthy cognitive function with age and even slow its decline.

Menopausal 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 WHIMS, a substudy of the WHI, contradicted these previous findings. The WHIMS results suggest that women age 65 and older receiving either estrogen alone or PremproTM (a particular form of estrogen plus progestin hormone therapy) could be at increased risk of developing dementia, including AD. Because of these 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, menopausal hormone therapy may have other beneficial health effects in some women and remains in wide use. NIA-supported investigators continue to study the effects of menopausal hormone therapy on cognition, as well as the mechanisms through which estrogen and related hormones work on the brain.

Effects of Hormone Therapy and Exercise on Cognition in Postmenopausal Women

In a recent study, investigators found that women who received menopausal hormone therapy for less than 10 years retained healthier gray matter in the brain's prefrontal cortex, an area of the brain important for problem-solving, emotion, and complex thought, and exhibited better performance on measures of executive function (i.e., the capacity to control and apply one's mental skills). A regimen of longer than 10 years was associated with increases in prefrontal cortex deterioration and amplified decline of performance on executive functioning tasks. However, the investigators also found that high fitness levels augmented the beneficial effects of the shorter regimens while ameliorating the negative effects of longer-term treatment.

Effects of Combination Estrogen plus Progestin Hormone Treatment on Cognition and Affect: Findings from the WHISCA

In a recent study of participants in the WHI, which was co-funded by the NIH ORWH, investigators found that combination hormone treatment with estrogen plus progestin had a negative impact on verbal memory (remembering a shopping list) and a positive trend on figural memory (reproducing designs) over time compared with placebo. Other cognitive domains were not affected. Both effects on memory were evident only after long-term therapy (four to five years of treatment); the first cognitive assessment, which was performed after three years of treatment, did not show significant differences between treated and untreated women. Combination hormone treatment did not significantly influence mood or symptoms of depression. These findings indicate that hormone treatment may have modest but complex effects on the brain.

Estrogen Therapy Protects Against Stroke-related Injury in an Animal Model

Researchers have found that estrogen therapy protects against stroke-related brain injury in young and aging female rats, possibly by influencing the activity of genes that suppress cell death mechanisms. Further studies are needed to determine whether estrogen therapy initiated during the perimenopausal period in women could delay or even prevent stroke or other neurodegenerative diseases.

Osteoporosis

It is estimated that 10 million men and women currently have osteoporosis, and an additional 34 million have low bone mass and are at risk. One in every two women over age 50 will have an osteoporosis-related fracture in her lifetime.# Treatment options for women have most often included hormone therapy involving estrogen; however, recent clinical evidence has indicated that estrogen therapy may have undesired side effects on other organs.

Follicle-stimulating Hormone as a Primary Regulator of Osteoporosis

Recent studies have shown that increased circulating levels of FSH, which is associated with the loss of estrogen at menopause, are predictive of bone loss in women. For example, one recent study, which received support from the ORWH, examined the association between reproductive hormones and bone mineral density (BMD) around the menopausal transition. Investigators found that baseline FSH concentrations, subsequent FSH levels, and their interaction predicted four-year BMD loss. Spine and hip BMD losses during the menopausal transition were most strongly related to the interaction between initial FSH levels and longitudinal FSH changes and other hormonal levels or changes.

Now, findings from a study in a mouse model suggest that increased levels of FSH may, in fact, directly influence menopause-related bone loss. In this study, mice with lower levels of FSH or with half the normal level of the FSH receptor did not lose bone but actually gained bone. FSH appears to increase the activity of osteoclasts (cells that resorb bone), thus increasing the loss of bone and the development of low bone density and osteoporosis. This is the first time FSH has been demonstrated to have an effect on bone, and this study points to a logical mechanism for a direct role of elevated FSH levels in bone loss at menopause. The emergence of FSH as a potentially powerful player in bone loss at menopause provides important information about the etiology of the disease and also opens up a new

area for potential treatments. Methods to lower or interfere with the actions of FSH in stimulating osteoclast activity may lead to new ways to prevent and treat osteoporosis.

Kyphosis and Fracture Risk

It is unknown whether kyphosis (a type of abnormal curvature of the thoracic spine) is an independent risk factor for subsequent osteoporotic fractures. In a recent study, increases in kyphosis were associated with increases in fracture risk throughout the body, independent of previous history of fractures or BMD. Whereas hyperkyphosis may often result from vertebral fractures, the study findings suggest that hyperkyphotic posture itself may be an important risk factor for future fractures, independent of low BMD or fracture history.

Vitamin D3 Supplementation in African American Women

The interactions of vitamin D and calcium intake in protecting against bone loss are not completely understood. Specifically, it is not known if vitamin D increases bone protection if calcium intake is at levels generally considered adequate. A recent clinical trial tested whether vitamin D3 supplementation would prevent bone loss in postmenopausal African American women with sufficient calcium intake. After three years, there were no differences between the vitamin D and control groups on bone loss or bone turnover markers. Further studies are needed to determine whether these findings are applicable to women in other ethnic groups.

Racial Disparities in Osteoporosis

For unknown reasons, fewer African American women experience osteoporosis-related fractures than white women. Investigators examined the extent to which differences between black and white women in overall calcium intake might contribute to this disparity. They noted no overall difference in daily supplemental and dietary calcium intake, but older African American women received more calcium from grains and less from dairy than their matched white counterparts. In a second study, the investigators examined physical activity on differences in osteoporosis by conducting bone mineral density tests and ultrasounds on a sample of matched African American and white females. Overall, African American women had higher bone mineral density on all measured locations when compared with white women, although white women reported higher physical activity.

Reproductive Health and Menopause

The hormonal changes that accompany the menopausal transition have important ramifications on health and quality of life beyond the reproductive system, not only at midlife but well into old age. For example, sex hormones, such as estrogen, are implicated in bone and cardiovascular health; the role of estrogen in cognitive health continues to be elucidated.

The SWAN

The NIA's major study of the menopausal transition is the SWAN, which evaluates longitudinal changes in biological, behavioral, psychosocial parameters in women as they transition from pre- to postmenopause. The SWAN is co-funded by the NINR and the NIH ORWH. Major findings from SWAN in FY 2005 and 2006 include:

- **Hormonal Changes and Vasomotor Symptoms**
  Although it is widely believed that estrogen deficiency is the cause of vasomotor symptoms (VMS), such as hot flashes, recent findings indicate that only follicle stimulating hormone (FSH) is associated with both the prevalence and frequency of vasomotor symptoms in women at midlife.
- **Predictors of Vasomotor Symptoms**
  In one of the few studies to examine VMS across several years among a multiethnic group of women, SWAN investigators found that reports of VMS increased dramatically as women progressed from premenopause to early perimenopause and even more dramatically as they made the transition to late perimenopause. In fact, menopausal status (pre-, peri-, or postmenopause) was the strongest predictor of VMS. The group also found that, compared with white women, significantly more African American women and fewer (although not significantly fewer) women from the other three racial/ethnic groups reported VMS.

- **Sleep and the Menopausal Transition** The likelihood of reporting trouble sleeping was 29 percent higher in perimenopausal than in premenopausal women. Mood and VMS were the strongest and most consistent contributors to trouble sleeping. The most trouble sleeping was observed at the beginning and end of the menstrual cycle.
- **Pain and the Menopausal Transition** Prevalence of aches and pains was high, with one in six women reporting daily symptoms. Compared with premenopausal women, those who were early perimenopausal, late perimenopausal, or postmenopausal reported significantly more aches and pains in age-adjusted analyses.

Female to Male Partial Sex Reversal in Mice Lacking Foxl2

The Foxl2 gene is mutated in some patients with premature ovarian failure, a condition that occurs in approximately 250,000 women under the age of 40 in the U.S. and causes a number of symptoms, including infertility.# In a recent study, investigators found that genetically female mice that lack Foxl2 can form oocytes (eggs), but shortly after birth their ovaries take on the genetic—and some structural—characteristics of testes. This surprising finding suggests that Foxl2 action may be necessary to repress activity of the male gene pathway both before and after birth and that Foxl2 may be the long-sought "repressor" of maleness that opposes the male sex-determining gene Sry.

Anti-Marinobufagenin as an Antihypertensive Agent in Preeclampsia

Preeclampsia is a condition characterized by elevated blood pressure and protein in the urine that complicates approximately 8 percent of pregnancies in the U.S.# Marinobufagenin (MBG), a steroid that increases blood pressure, is implicated in preeclampsia. NIA investigators have developed several monoclonal anti-MBG antibodies (Mabs) and tested them in a rodent model of preeclampsia. The Mabs were successful in lowering the rats' blood pressure. Further research is needed to determine the safety and efficacy of Mab treatment in women.

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

The menstrual cycle is maintained through precisely calibrated interaction between the brain and the ovaries. After the final menstrual cycle, there is a marked decline in estrogen (E) levels. Leading up to this event, changes in menstrual cycle regularity and hormonal patterns occur, as does an increase in symptoms, such as hot flashes and night sweats. In one recent study, which was co-funded by the ORWH, investigators observed different patterns of hormone fluctuations among perimenopausal women. In one group of women, E levels increased in the early part of the cycle, as is normal among premenopausal women, and this was followed by a surge of luteinizing hormone (LH) —the usual and expected response. In the second, the E levels increased as usual, but LH levels did not. In the third group, E levels did not increase as the cycle progressed, and there was no LH surge, but LH levels were higher for most of the cycle. The women in the third group had significantly more hot flashes and night sweats than those in the other two groups. These findings: (1) suggest that a specific hormonal pattern linked to increased hot flashes reflects alterations in the sensitivity of the brain to estrogen; and (2) provide new clues about hormone influences on hot flashes and night sweats as women approach menopause.

Gender Analysis

Smoking Accounts for Reduction in Sex Differentials in Mortality at Older Ages and the Reduction Is Likely to Continue

Between 1948 and 2003, sex differentials in mortality at older ages in the U.S. first widened and then narrowed. This pattern reflected striking differences between the sexes in the timing of improvements of mortality. For older men, rates improved only slowly during the period 1948 to 1958 and rapidly during the period 1978 to 2003. In contrast, for older women, improvement was rapid in the 1950s but slow in the 1980s and 1990s.

Researchers assembled estimates from several sources on the smoking experience of successive birth cohorts of American men

and women, from those born in the 1890s through those born in the 1950s, and related them to five-year changes in all-cause mortality as the cohort passed through ages 50 to 83. Their data indicate that currently women have a 54 percent higher probability than men of surviving from age 50 through 83. If smoking were eliminated, researchers estimate that the differential would narrow to 15 percent. Based solely on differences in smoking history for more recent birth cohorts, the model projects continued mortality improvement (a 23 percent increase in survivorship from age 50 to age 83) for men but almost no improvement from this source for women since men have reduced smoking in recent years while women's smoking has changed little.

The Paradox of Greater Disability but Longer Survival for Women

Women have worse self-rated health and more hospitalization episodes than men, but they have lower mortality rates than men at every age from adolescence to late middle age. Some explanations for this paradox focus on presumed gender differences in willingness to report health conditions and discuss them with interviewers or with health professionals, with men considered to be "stoics." Other explanations focus on possible differences between men and women in both prevalence and severity of particular chronic conditions. While women may have conditions, such as arthritis or headaches, which can be debilitating though not associated with high risk of mortality, men may be more likely to suffer from cardiovascular and respiratory conditions, which pose significantly increased mortality risk.

Investigators recently attempted to disentangle this paradox using 14 years of survey data on self-rated health and hospitalizations for more than 385,000 men and women between the ages of 45 and 84. They found that, contrary to previous hypotheses, men and women appear not to use different standards for assessing their own health; the difference in self-assessed health between women and men can be entirely explained by differences in the distribution of conditions. While men had better self-rated health, on average, than women, women and men with the same sets of chronic conditions had the same self-rated health, thus disproving the "men are more stoic" hypothesis. Poor health is equally predictive of hospitalization for both men and women, which suggests that hypotheses about men's unwillingness to seek treatment are likewise invalid as explanations for gender differences in health care utilization. There were important differences in the severity of the conditions leading to hospitalization: men with respiratory cancer, cardiovascular disease, and bronchitis are more likely to be hospitalized and, therefore, experience a more severe form of the ailment than women with the same condition. Differences in the distribution of chronic conditions do not fully explain the mortality differences between men and women as men still have higher mortality rates even after the distribution of conditions has been taken into account. This research contradicts some of the common hypotheses on gender differences.

Primary Care Doctors May Not Diagnose and Manage Coronary Heart Disease as Actively for Women as for Men

Previous studies have established that women are less likely than men to receive thorough diagnostic investigations and surgical treatments for coronary heart disease (CHD). Few studies have focused on the exact points in the process at which disparities arise (e.g., initial access, interactions with physicians, hospitalizations), and few have examined the possibility of age-by-gender interactions in the process. In a recent study, investigators trained professional actors to portray patients on videos in realistic first consultations with a doctor, presenting with symptoms either of CHD or depression. Participating primary care physicians (256 selected randomly in Massachusetts and two regions in England) watched the seven to eight minute tapes and answered questions about how they would diagnose and manage the patient.

In the two countries combined, physicians reported fewer followup questions for women (mean 5.7) than for men (7.0); proposed fewer examinations for women (4.3 compared with 5.1); proposed fewer diagnostic tests for the CHD diagnosis (80 percent for women vs. 90 percent for men); and were less likely to prescribe medications appropriate for treating heart disease for women than for men (52

percent of women vs. 64 percent for men). In both countries, the female patient reported to be age 55 was less likely to have a medication prescribed, and doctors were less sure of the CHD diagnosis in women than for men the same age. But even with less certainty, English (though not American) doctors reported that they would ask fewer questions of the woman aged 55 than of a man and fewer than for a woman aged 75. The black patients and those portraying working-class men and women were not treated differently than white and middle-class patients in these simulations.

This analysis was based on "video vignettes," and the correspondence of self-reports to actual behavior is unknown, as is the clinical significance of differences in diagnosis and management after a first consultation. But the finding of significant differences between the diagnostic and management activities that physicians think appropriate for women and for men, at least in England, warrants further research.

Sex Differences in the Emergency Department Evaluation of Elderly Patients with Syncope

This study assessed the impact of sex on the frequency of syncope (fainting) and the rate of identifying a specific etiology among elderly patients. Among patients older than 65 years presenting with syncope to a large urban teaching hospital, men were more likely to have comorbid conditions, including coronary artery disease, prior myocardial infarction, and diabetes mellitus, than were women. However, women were significantly more likely to present to an emergency department with syncope yet were less likely to be discharged with a defined etiology.

Other Research Accomplishments

Depression May Be an Important Modifiable Mediator of Cardiovascular Disease in Middle-Aged Women

Depressive symptoms are a risk factor for CHD in healthy adults, as well as for recurrent events in those with established CHD. However, whether depression is an accompaniment or an antecedent to CHD is unclear. To determine whether middle-aged women with a history of recurrent major depression would be at increased risk of atherosclerosis, coronary and aortic calcification was measured in 210 healthy, middle-aged women without known coronary disease. The women were also screened for symptoms of clinical depression. Even after adjustment for cardiovascular risk factors and socio-demographic characteristics, compared with a single episode or no history, women with a history of recurrent major depression were significantly more likely to have any coronary calcification or calcification in the high category at either site compared with women reporting a single episode of depression or no depression. Menopausal status was unrelated to depression or the calcification. The findings from this study, which received support from the ORWH, suggest that a promising avenue of future research to reduce the risk of atherosclerosis may be to exploit potentially modifiable aspects, such as reducing depressive episodes which may underlie or promote the development of cardiovascular disease in women.

Free Androgens and Sex Hormone Binding Globulin in Perimenopausal Women Predict and May Mediate Cardiovascular Disease

On average, the onset of cardiovascular disease (CVD) in men precedes that in women by more than 10 years. Until recently, scientists attributed this discrepancy to the protective effects of naturally occurring estrogen in women; however, recent clinical trial results demonstrating that menopausal hormone therapy does not reduce the risk of coronary heart disease in women suggest that this long-held hypothesis is incorrect. Researchers are now studying androgens and sex hormone-binding globulin (SHBG) as potential mediators of increasing CVD risk in women at midlife. To evaluate the relationships between reproductive hormones and CVD risk factors, testosterone (T) and estradiol (E2) were evaluated along with SHBG and the free androgen index (FAI) (e.g., the amount of T not bound by SHBG) among SWAN participants. Low SHBG and high FAI were strongly and consistently related to elevated CVD risk factors (e.g., higher insulin, higher glucose, and adverse lipids) even after controlling for body mass index. Low levels of E2 were associated with elevated CVD risk factors to a lesser degree.

These observations were consistent across the five ethnic groups studied. The results from this study, which was co-funded by the ORWH, suggest that SHBG and FAI factors may play a significant role in the CVD risk profile of perimenopausal women.

The Intact Ovary Facilitates Atherosclerotic Reduction in Response to Estrogen

Virtually all studies of estrogen therapy in rodent and monkey models use animals whose ovaries have been removed, an approach that is most expeditious in terms of experimental protocol. However, in a recent study, atherosclerosis was induced in mice that either had their ovaries removed or were subjected to a chemically induced menopause (but retained their ovaries). The mice were then treated with estradiol (a form of estrogen). Investigators found that atherosclerosis was reduced in both groups of animals but more reduced in those with intact ovaries. In addition to suggesting a role for the ovary in heart disease prevention even after menopause, this study presents opportunities to understand underlying biologic mechanisms of the role of the intact ovary in this protective estrogen response.

Risk Factors for Falls in Older Disabled Women with Diabetes

Many clinical and epidemiological studies have shown that diabetes mellitus is strongly associated with a large burden of physical disability, including risk of falling. In a recent study of older disabled women, investigators found that that the excess risk of falling associated with diabetes mellitus was larger in women with pain and higher BMI compared with those without these conditions. These findings have important implications for improved clinical management of older diabetic persons.

Gender and Socioeconomic Trends in Bariatric Surgery

Morbid obesity is a serious health concern, with bariatric surgery being the most effective treatment. Investigators recently detailed trends in bariatric surgery from 1998 to 2003 and found that women underwent the surgery at a far greater rate than men (80 percent of surgeries were for women) that was not proportional to rates of obesity. Furthermore, there is an inverse association between obesity and socioeconomic status that is not reflected in rates of bariatric surgery. Poor people are more likely to be obese but are less likely to be recipients of the surgery. Accordingly, most surgery recipients had private health insurance.

Vitamin D and Calcium Supplementation May Reduce Falls in Older Women

In a recent study, long-term dietary vitamin D and calcium supplementation was found to be effective in reducing falls in ambulatory older women and especially in less active women. Men appear to differ in their response to this treatment; the intervention had no significant effects independent of their physical activity level. Because supplementation with calcium and vitamin D is simple and inexpensive and is associated with relatively few side effects, efforts to reduce falls and improve skeletal health in older persons should incorporate an emphasis on calcium and vitamin D supplementation.

Ethnic Differences in Breast Self-examination Rates

Investigators questioned more than 1,300 women representing six ethnic groups (European American, African American, Haitian, Dominican Hispanic, English-speaking Caribbean, and Eastern European) regarding their breast self-examination (BSE) cancer screening practices. They found that BSE performance differed significantly by ethnic group, with 84 percent of Dominicans but only 31 percent of the Haitians interviewed having practiced BSE in the past month. In general, perceived efficacy of BSE predicted its use; "cancer worry" predicted BSE in some but not all ethnic groups. Interestingly, women of African descent but from different ethnic groups differed significantly in their screening habits and predictive factors. These findings suggest that educational materials tailored to specific ethnic groups may be needed in order to increase BSE in the population.

Screening for Translocations That Lead to Premature Ovarian Failure

Because the pool of ovarian follicles is established during fetal life, the development of the ovary predetermines female reproductive

life span. Usually, menopause occurs at about age 50; but in up to 5 percent of women who have lower than usual numbers of follicles, premature ovarian failure (POF) ensues before age 40. Many cases of POF result from genetic changes, including mutations in the Foxl2 gene, which appears to be a master gene involved in follicle development and in the maintenance of female sex in the ovary. NIA intramural investigators are planning to screen systematically for additional potential sites of genetic mutation in women or families that show a tendency toward POF as a first step in defining additional genes that may be altered to cause the early menopause. Approximately 20 such sites may be identified per year, and the investigators will study these sites as a source of additional candidate genes with a role in the programming of the reproductive life span.

Initiatives

Request for Applications (RFAs)

- **Biology of the Perimenopause: Impact on Health and Aging in Non-reproductive Somatic and Neuronal Tissues**
  The goal of this RFA was 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. The focus was on: (a) how hypothalamic-pituitary-ovarian (H-P-O) axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within various tissues; (b) the role of steroid hormone biosynthesis and/or metabolism on pathophysiologic processes across the menopausal transition; and (c) the role of aging on these pathophysiologic processes. (RFA-DK-05-014)
- **Improving Measurement Tools For Sternal Skin Conductance and Hot Flashes: Phase I SBIR**
  The purpose of this initiative, co-funded by the NCCAM, the NIBIB, and the NIH ORWH, was to support research to improve measurement tools or devices for sternal skin conductance to monitor hot flashes. Improved measurement tools that are reliable, user-friendly, and reasonably priced and that can collect data for extended periods of time are needed to evaluate the efficacy of interventions to reduce hot flashes under unsupervised, ambulatory conditions in clinical studies. Following a successful development stage, one or more devices will be employed in a small clinical trial to evaluate an intervention for the treatment of hot flashes.

Conferences and Workshops

- **Management of Menopause-related Symptoms**
  The NIA and the NIH OMAR sponsored a State-of-the-Science (SoS) Conference on Management of Menopause-Related Symptoms in March 2005. During the conference, experts presented information on the biology of the menopausal transition, the nature of the symptoms women experience, and strategies for relieving the common problems associated with the menopausal transition. After weighing all of the scientific evidence, including the data presented by the speakers, as well as a thorough review of the English-language literature, an independent panel prepared and presented an SoS statement (see http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025main.htm).

As a followup to this meeting, the NIA initiated an action plan to seek input from extramural researchers in order to help prioritize the intervention-related research recommendations for implementation. In collaboration with the NCCAM, the NICHD, the NIH ORWH, the NIMH, the NIH ODS, and the NCI, the NIA convened a panel of 11 investigators with expertise in reproductive endocrinology, the epidemiology of and mechanisms responsible for menopause-related symptoms, quality of life issues, management of menopause-related symptoms, complementary and alternative medicine, and clinical trials design and methodology. Representatives from the FDA also participated. This panel of experts met on July 11-12, 2006 for the first of two

meetings that had the following two goals: (1) review the statement of the independent panel of the March 2005 NIH SoS Conference on Management of Menopause-Related Symptoms; and (2) make recommendations as to the next steps to be undertaken by interested NIH Institutes and Centers with respect to identifying priorities and promoting new opportunities for research. Such priorities and opportunities would be focused on developing and/or testing current or new interventions to reduce the burden of a number of menopause-related symptoms (to be identified by the panel). The second meeting of the panel took place on November 20-21, 2006, and an executive summary of panel's deliberations and recommendations is currently in development.

Ongoing Research Initiatives

- **SWAN**
  The SWAN is an ongoing cohort study evaluating longitudinal changes in biological, behavioral, psychosocial parameters in women as they transition from pre- to postmenopause. It is of high relevance to understanding healthy aging in midlife women and beyond. The goal of the 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, the SWAN is a cooperative agreement consisting of seven clinical field sites and a central reproductive hormone laboratory. Coordination is supported by the NIA, the NINR, the NCCAM, and the ORWH.
- **WHISCA**
  The WHISCA project is an ancillary project of the WHIMS and the 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. Although study therapies have been terminated in the WHI, NIA investigators continue to follow women through the WHISCA extension study to assess the long-term effects of hormone therapy on age-related cognition changes in women.
- **WHAS**
  There are two separate but complementary WHAS. The first, an intramural initiative of the NIA, was planned to determine the causes and course of disability and opportunities for its prevention in these moderately to severely disabled older women. This study ended in 2002. WHAS II, conducted with NIA support, evaluates older women who were among the two-thirds least disabled in the community at baseline, to understand the natural history and etiology of disability onset. The study, funded since its inception by the NIA, seeks to determine the factors that precipitate disability and whether there is a preclinical stage of disability in mobility that identifies those who will go on to have difficulty in these areas. Although recruitment for WHAS I and II has ended, data analyses in a number of areas are ongoing.

Health Disparities among Special Populations of Women

The health status of racial and ethnic minority groups in the U.S. 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 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 NCMHD. 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:

- The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS), a community-based study designed to focus on evaluating health disparities in minority and socioeconomically diverse populations;
- A study of health services and outcomes in elderly African American women;
- A study of gender, age, and ethnicity in the management of chronic illness; and
- A study to investigate the extent of disparities in health trends by race/ethnicity, sex, and socioeconomic status.

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. It is estimated that there are 18 million alcohol-abusing or alcohol-dependent individuals in the U.S., of which more than 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's health. Research related to women's health is found in each programmatic division of the Institute. Because of the multidimensional and multidisciplinary nature of alcohol use disorders and their prevalence worldwide, collaborative research endeavors on a national and international scale are required for progress toward the goals of reducing alcohol abuse disorders and alcoholism among women. Significant scientific advances in understanding the causes, consequences, prevention, and treatment of alcohol use, abuse, and dependence among women have occurred in the past two fiscal years. This report addresses research on women and alcohol along six central themes: (1) epidemiology of women's drinking; (2) gender differences; (3) alcohol and pregnancy; (4) alcohol use and fetal alcohol spectrum disorders; (5) treatment of women with alcohol use disorders; and (6) violence and other social consequences of alcohol abuse. In addition, chronic fatigue syndrome (CFS), a disorder predominantly of women, in the context of alcohol use disorders is a new area of focus for the Institute.

Trends in heavy drinking among women continue to decline with increasing age, as does overall drinking, mirroring trends in the general population. However, patterns of drinking (quantity/frequency) indicate that binge drinking, particularly among younger women, is problematic. Women are more susceptible than men to the adverse consequences of alcohol. Furthermore alcohol affects men and women infected with the hepatitis C virus (HCV) differently. Epidemiologic studies provide evidence that heavy drinking contributes to HCV-related disease progression and death. Heavy-drinking, HCV-infected women died more than a decade earlier than HCV-infected women who drank only moderately or not at all. Women with HCV who drink heavily squander their normal survival advantage over men with the same infection.

Preclinical studies in animal models have begun to reveal the mechanistic basis underlying gender differences in alcohol-induced organ damage. Studies of alcoholic liver disease have shown that alcohol increases the activity of inflammatory proteins within the liver, an effect that is modulated differently by estrogen or testosterone. Female rats had a heightened inflammatory response compared with male rats, which could, in part, account for their enhanced susceptibility to liver damage. Chronic ethanol (alcohol) abuse is correlated with osteoporosis. Hormonal supplementation with estradiol seems to afford a measure of protection against ethanol-induced bone loss in female rats, perhaps by augmenting the activity of bone-forming cells.

Research has firmly established that maternal alcohol consumption can lead to fetal alcohol syndrome (FAS), the leading preventable cause of mental retardation. A study conducted in several urban and rural communities in South Africa in mothers of grade school children with FAS confirmed that drinking before, during, and after pregnancy was associated with lower IQ and behavioral problems in their children. The NIAAA support for the Collaborative Initiative on FAS and fetal alcohol spectrum disorders (FASD) is expected to lead to new insight into the underlying mechanisms of these disorders and development of therapeutic interventions to provide relief to those affected with the most debilitating features of the disease. Multiple international sites with a high incidence of FAS and FASD are participating in this important study, including a cooperative agreement with the Moscow Region Ministry of Health to screen more than 26,000 pregnant women and select a sample of offspring for longitudinal follow-up. A cooperative agreement was established jointly with the NICHD to conduct community-linked studies to determine the underlying causes of sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and FASD, and the role of prenatal alcohol exposure. The long-term goals of this initiative are to decrease fetal and infant mortality and to improve child health in the affected communities.

Identification of women at risk for children with FASD has been challenging. T-ACE (tolerance, annoyed, cut down, eye-opener) was developed specifically to screen for alcohol problems in pregnant women and has been validated as more accurate and sensitive than previous instruments. Using the T-ACE instrument, investigators have shown that, contrary to what might be expected, social support during pregnancy was not predictive of subsequent prenatal alcohol use. Moreover, women's knowledge of healthy pregnancy habits had only a weak relationship with prenatal alcohol consumption. These results provide evidence that specific knowledge about the risks associated with prenatal drinking alone is insufficient to change behavior; therefore, universal screening of all pregnant women is recommended. Screening to reduce risky drinking among nonpregnant women of child-bearing age may also be advisable as a way to identify women in this age group who would benefit from counseling.

Alcohol abuse in risky environments is associated with a women's ability to make and effect decisions regarding their health and welfare, such as the right to refuse unsafe sexual practices. A recent study shows that alcohol consumption increases consent; however, assertive resistance increases as the level of sexual aggression escalated. Even at a relatively high level of alcohol consumption, a woman can understand the threatening nature of the situation. Childhood trauma was a major predictor of vulnerability to sexual assault. An ongoing randomized clinical trial is focusing on reducing HIV risk behaviors among women seeking help for alcohol problems. It is anticipated that women who respond favorably to alcohol treatment and who receive 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 receiving standard risk reduction interventions.

In summary, scientific research continued in FY 2005 and 2006 on gender-based differences in the causes, consequences, prevention, and treatment of alcohol use disorders. A new area of research emerged, involving a partnering between the NIAAA and the ORWH on CFS. One initiative focused on the epidemiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the life span. The objective of a second initiative was to elucidate the interactions of neural and immune systems in the CFS disease process and to determine how alterations in physiological systems affect the progression and manifestation of CFS. The NIAAA, the NIDA, and the SAMHSA co-sponsored a conference on women, addiction, and recovery. The conference was designed to advance the field of women's substance abuse treatment by presenting the latest research and discussing how it can be applied to improve clinical practice and service delivery for women with substance use disorders. Ultimately, long-term structural changes in women's social status in the effort to reduce maladaptive behavioral strategies including alcohol consumption and alcoholism, and their biomedical and behavioral consequences are needed.

Accomplishments

Epidemiology of Women's Drinking

The NIAAA has looked at historical and age-related trends in patterns of drinking among women in the U.S. A study using national survey data from 1981 to 2001 examined 12-month drinking trends among women and showed increased rates of 30-day abstinence rates, declines in heavy drinking episodes, and declines in overall drinking with increasing age. Two trends were noted when comparing women in the 2001 sample to women in the 1981 sample. First, women drinkers under age 50 reported a higher prevalence of intoxication in the later survey than in the earlier. Second, women in their twenties were more informed about the adverse effects of alcohol use and drinking in less hazardous ways in the 2001 survey compared with women in the 1981 survey. This study provides evidence that the rates of alcohol consumption are declining for women in the general population and supports the value of public health messages regarding alcohol consumption.

Gender Differences

Women's Susceptibility to Alcohol Effects

Epidemiological studies have shown that women are more sensitive to the adverse effects of alcohol than men; the incidence of alcohol-induced liver injury is higher and disease progression is faster among women than among men. A recent study based on mortality data compiled by the National Center for Health Statistics demonstrates gender effects in mortality rates when male and female alcohol abusers infected with HCV were compared. Women with HCV who drink heavily squander their normal survival advantage over men with the same infection. Heavy-drinking, HCV-infected women died more than a decade earlier than HCV-infected women who drank only moderately or not at all. The mean age of death was shortened by five years in males (from 55.1 to 50.0) but by almost 12 years among females (61.0 to 49.1). The findings strengthen the hypothesis that alcohol affects men and women differently and provides further evidence that heavy drinking contributes to HCV-related disease progression and death, an effect more pronounced in women than in men.

Gender Differences in Inflammation May Mediate Susceptibility to Liver Injury

It is well known that women are more susceptible to alcoholic liver disease (ALD) than men, but the reason is not known. One possibility is differential responses in inflammatory processes leading to liver injury. Preliminary studies in rats show that female rats have greater activation and higher levels of the receptor for IL-6, a protein that promotes inflammation and is a marker for ALD in humans. High receptor levels would suggest greater inflammatory activity. On the other hand, male rats have higher levels of IB, an inhibitory signaling molecule that may downregulate the expression or function of the receptor, thus resulting in dampened inflammatory activity. A small followup project was funded in FY 2006 to investigate the interactions between estrogen or testosterone and this inflammatory pathway and their effects on liver injury.

Gender and Adolescent Alcohol Use Disorders

Alcohol use differentially affects brain functioning in male and female adolescents, but the underlying mechanism is not known. To gain a better understanding of this difference, 14- to 17-year-old adolescents with alcohol use disorders (AUDs) and control adolescents without AUDs performed spatial working memory and vigilance tasks during functional magnetic resonance imaging. Gender, AUD, and their interaction were significantly associated with brain activation patterns for the tasks. There were interactions in the superior frontal, superior temporal, cingulate and fusiform regions; female and male adolescents with AUDs showed a different brain response from each other and from the control subjects. Overall, female adolescents with AUDs showed a greater departure from normal activation patterns than male adolescents with AUD. Although this study was conducted with a relatively small sample, it does indicate that adolescent alcohol involvement may affect male and female brains differently and that adolescent females may be somewhat more

vulnerable to adverse alcohol effects. With continued drinking, these adolescents may be at an increased risk for behavioral deficits.

Alcohol and Pregnancy

Prenatal Alcohol Exposure among High-risk Populations: Relationship to Sudden Infant Death Syndrome and Stillbirth

A cooperative agreement was established jointly between the NIAAA and the NICHD to conduct community-linked studies on the underlying causes of sudden infant death dyndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome (FAS), and the role of prenatal alcohol exposure. The Prenatal Alcohol in SIDS and Stillbirth (PASS) Network consists of two comprehensive clinical sites in the Northern Plains and Western Cape of South Africa, a developmental biology and pathology center, a physiology assessment center, and a data coordinating and analysis center. In FY 2006, the NICHD and the NIAAA funded the next phase of the PASS Network, which will include a comprehensive longitudinal cohort study of 12,000 pregnant women and their infants, who will be followed until one year of age. Some embedded studies have been designed to explore the role of (under-) nutrition in exacerbating the effects of maternal alcohol exposure on fetal and offspring development. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities.

Placental Biomarkers of Alcohol Exposure

A clinical biomarker to detect maternal drinking during pregnancy is desirable, not only to facilitate intervention efforts to prevent maternal drinking but also to aid in the early diagnosis of FAS and alcohol-related neurodevelopmental disorders. Technologies that can detect patterns of change in the expression of genes, proteins, or metabolites in response to disease states are powerful tools to identify biological markers. Alcohol consumption results in significant changes in the protein expression profile (proteomics) obtained from placentas of pregnant rats. Once proteins that are altered by alcohol exposure are identified, more detailed studies of the relationship of protein change to alcohol dose and consumption patterns can be conducted, and biomarker sensitivity and specificity can be determined. This translational research will set the stage for biomarker studies in human placentas. In the absence of alcohol-induced physical effects at birth, such a biomarker could provide an early indication that a newborn is at risk for developmental disabilities later in life.

Ethanol Consumption and Bone Loss during Pregnancy

Chronic ethanol abuse is correlated with osteoporosis, decreased bone mass, and increased risk of fractures in women. The added metabolic demands of pregnancy and lactation result in increased material bone turnover and decreased bone mass. The effects of alcohol consumption on bone mass and mineralization during pregnancy have not been investigated in detail. A recent NIAAA-supported study in an animal model has shown that bone loss associated with pregnancy is markedly exacerbated by ethanol consumption. These ethanol-induced skeletal deficits during pregnancy could not be attributed to inadequate dietary intake since the animals received complete parenteral nutrition. Alcohol appears to inhibit bone formation during a period of high bone turnover.

Alcohol Use and Fetal Alcohol Spectrum Disorders

Collaborative Initiative on Fetal Alcohol Spectrum Disorders

Ongoing research within this consortium comprising multiple international sites with high incidence of FAS and fetal alcohol spectrum disorders (FASD) includes a cooperative agreement with the Moscow Region Ministry of Health to screen more than 26,000 pregnant women. A sample of heavy drinkers and controls will be selected for longitudinal followup of the offspring. An embedded study examines the effects of maternal micronutrient supplementation on the growth, neurobehavioral development, and alcohol-related physical features of the alcohol-exposed offspring. The long-term goals of this research consortium are to refine the diagnostic criteria for FAS/FASD, explore the underlying mechanisms

of the disorder, and develop therapeutic interventions to provide relief to those affected with the most debilitating features of the disease.

Maternal Risk Factors for Fetal Alcohol Syndrome: A Population-Based Study in South Africa

A comprehensive prevention study in five matched urban and rural communities in the Western Cape Province of South Africa that screened and diagnosed grade-school children for FASD and partial FASD found that mothers had a higher prevalence of current drinking and history of drinking during pregnancy when compared to control mothers. A significantly greater proportion of mothers of FASD children reported drinking before becoming pregnant than control mothers (92 percent and 25 percent, respectively), and more FASD mothers continued to drink throughout the first, second, and third trimesters of the index pregnancy. Although differences in current drinking patterns were not significantly different, the mean number of drinks consumed per week during pregnancy was significantly higher among mothers of FASD children when compared with control mothers. Higher reported levels of drinks per day were associated with poorer IQ and verbal scores among the FASD children, and heavier drinking (e.g., three drinks or more per drinking occasion) during pregnancy was associated with behavioral problems among the women's children. Characteristics of the mothers of FASD children included rural residence, farm worker status, lower height, weight, and head circumference, and body mass than control mothers. The predominant beverage of choice among these mothers was beer.

Treatment of Women with Alcohol Use Disorders

Prenatal Drinking and Social Support

Lack of social support during pregnancy may be associated with the prenatal use of alcohol. One study evaluated the degree, predictors, and consequences of social support in a cohort of pregnant women who scored two or more on the T-ACE (tolerance, annoyed, cut down, eye-opener), a four-item screening questionnaire for prenatal drinking. Regardless of social support, measures of previous, prepregnancy, and early pregnancy drinking were the most predictive factors for subsequent prenatal alcohol consumption in this sample. Maternal social support was not predictive of either subsequent prenatal alcohol use or newborn birth weight. These findings are consistent with results from some other research and underscore the importance of screening pregnant women for drinking.

Prenatal Drinking and Knowledge of Healthy Pregnancy Habits

This study examined the impact of a couple's knowledge about healthy pregnancy habits involving alcohol and substance use in the context of other factors previously identified to predict prenatal alcohol consumption. This study was conducted in a sample of pregnant women and their male partners. Although the couples demonstrated good knowledge overall, knowledge about pregnancy risks from the use of substances and alcohol was not as influential in prenatal drinking as the women's prepregnancy drinking. Women's knowledge of healthy pregnancy habits had only a weak relationship with prenatal alcohol consumption. While women's score on the healthy pregnancy facts assessment showed a relationship with household income, those with higher incomes drank more frequently in later pregnancy than those with lower incomes. These findings are consistent with results from previous studies that have found higher levels of drinking among women with higher incomes and provide further evidence that specific knowledge about the risks associated with prenatal drinking alone is not enough to change norms and actual behavior.

Prenatal Drinking: Self Report vs. Medical Record

In one study, physicians identified only 10.8 percent of women recognized by the T-ACE screening test as at risk for alcohol consumption during pregnancy. Given women with the same income, education, and prepregnancy alcohol consumption, physicians were 3.5 times more likely to identify nonwhite participants as being at risk for prenatal alcohol use than their white counterparts. More than 80 percent of those who the physicians did not consider at risk actually consumed alcohol during their pregnancy. These findings underscore the need for

universal screening of all pregnant women and for more efforts to increase physician sensitivity to problem drinking among women from all ethnic backgrounds.

Identifying Risk Drinking in Expectant Fathers

Identification of risk drinking in expectant fathers may be helpful in efforts to minimize maternal alcohol use and to inform them about a problematic practice during a critical developmental stage. One study compared the effectiveness of the T-ACE screening test with that of the Alcohol Use Disorders Identification Test (AUDIT) in the male partners of pregnant women who themselves were T-ACE positive. Although the AUDIT was better than the T-ACE as an independent predictor of risk drinking, the sensitivity and specificity of the T-ACE compared favorably with the sensitivity and specificity of the AUDIT when the tolerance threshold exceeded two drinks. These findings suggest that the T-ACE may be a practical way for clinicians to identify risk drinking in both pregnant women and expectant fathers.

Prenatal Drinking: Brief Intervention with Couples

A randomized trial of a single session, brief intervention for women recognized as at risk for alcohol consumption during pregnancy by the T-ACE screening test and their partners found that the effects of the brief intervention were significantly enhanced when a partner participated. Pregnant women with the highest levels of alcohol use reduced their drinking most after a brief intervention that included the partners. Factors associated with increased prenatal alcohol use after randomization included more years of education, extent of previous alcohol consumption, and temptation to drink in social situations. These findings suggest that patient-partner brief interventions may be effective for some women who drink heavily during pregnancy.

Screening and Brief Intervention for Problem-drinking Women

Early identification and intervention among problem-drinking women may avert the more severe adverse consequences of alcohol abuse and dependence. Among non-pregnant women of childbearing age, the use of alcohol and, in particular, the riskier practices of frequent and binge drinking, has not changed since 1995. An ongoing randomized trial is evaluating the effectiveness of screening and brief intervention to reduce risk drinking (i.e., exceeding the NIAAA sensible drinking limit of seven drinks per week or one to two drinks per episode) by non-pregnant 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 those receiving medical treatment as usual will achieve the 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 the NIAAA sensible drinking limits. Findings from this study will inform future recommendations regarding alcohol screening and interventions in general medical settings.

A pilot study within this project compared changes in drinking among a small group of infertile women who screened positive on the T-ACE questionnaire for at risk drinking and a second group of infertile women who were T-ACE negative. The T-ACE was found to distinguish between heavier and lighter patterns of alcohol use in this sample. Moreover, although the average quantity consumed per drinking day did not change in any of the groups, the overall mean percentage of days drinking declined significantly from the time of diagnostic assessment to followup in all groups. As in other treatment studies, the subjects seemed to respond therapeutically to assessment batteries, which in other circumstances might be considered to be the first step in treatment. More than half of the T-ACE-positive women who exceeded the NIAAA sensible drinking limits for non-pregnant adult women who were also seeking infertility treatment were not actively modifying their drinking behavior. This may signal a teaching opportunity for physicians to instruct their patients who may be otherwise unaware of the potential adverse impact of alcohol on fertility.

HIV: Substance Abuse, Sexual Risk, and Gender Inequality

A study of female sex workers in South Africa found that economic dependence on a main partner and traditional beliefs about a woman's right to refuse sex were associated with substance use before or during sex with that partner. Women with more progressive beliefs about gender ideology were better able to control their substance use in risky environments. These findings support a growing body of evidence that gender-based power differentials are critical factors in women's ability to make and effect decisions regarding their health and welfare. These findings point to the critical importance of long-term structural change in women's social status in the global effort to reduce the rate of HIV infection among women.

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 seventh grade and more than half by spring of the tenth grade. This study, involving parents and their eighth 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 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.

Violence and Other Social Consequences of Alcohol Abuse

Alcohol and Partner Violence

That alcohol consumption effects judgment is well known, as are the all-too-frequent unfortunate consequences for women. A detailed understanding of the decisionmaking process under the influence of alcohol is being investigated in several studies examining the impact of alcohol in the context of women's response to sexual aggression. A recent study examining the effects of alcohol consumption and type of relationship on women's responses to escalating male sexual aggression showed that alcohol consumption increases consent and interacts with type of relationship to increase passive resistance and with the level of sexual aggression to increase polite resistance. Assertive resistance increased and other responses decreased as the man's sexual aggression escalated. A history of childhood trauma lowered consent initially and increased passive resistance when rape was threatened. This study's findings indicate that, even at a relatively high level of alcohol consumption, a woman can understand when a man's actions are clearly assaultive and respond accordingly. Nevertheless, her alcohol consumption, in conjunction with her prior relationship with the man, can affect her actions in ways that can make her vulnerable to being sexually assaulted.

In other studies designed to better understand the role of alcohol consumption and vulnerability to sexual assault, women were recruited in bars and in classified ads. Women were classified as having a high or low breath alcohol concentration. They were then asked to project themselves into a hypothetical scenario that portrayed interest in establishing an intimate relationship. Women with higher breath alcohol concentration were found to perceive less risk in the scenario and anticipated less resistance than did women with low breath alcohol concentration. These studies suggest that the effects of alcohol on resistance are partially mediated via risk perceptions. Alcohol appears to reduce intentions to resist sexual advances from an acquaintance while increasing intentions to pursue relationship-enhancing behaviors.

A survey of female college students examined the psychological sequelae of child sexual abuse and the factors that contributed to revictimization in the form of adult sexual assault. Results indicated that individuals reporting both child sexual abuse and adult sexual assault were more likely to use alcohol and drugs to cope, act out sexually, withdraw from people, and seek therapy services. In addition, revictimized women reported more self-blame at the time of the abuse and currently. Individuals who engaged in these maladaptive coping responses were almost twice as likely to be revictimized as individuals who did not use these responses.

Cooperative Projects between the NIAAA and the ORWH

Chronic fatigue syndrome (CFS) is characterized by fatigue, malaise, and sleep and autonomic disturbances. It is thought to be associated with neuroimmune dysregulation that is exacerbated by stress, but the etiology is unknown. Two exploratory projects were funded in FY 2006 in response to the ORWH's initiative to elucidate neuroimmune mechanisms involved in the pathogenesis of CFS.

Neuropeptide Y (NPY): A Potential Biomarker of CFS?

NPY is involved in the regulation of many physiological and pathophysiological processes in the cardiorespiratory, immune, nervous, and endocrine systems. The protein can be measured in plasma. One project will explore the possibility that NPY could serve as a biomarker useful in diagnosis of CFS, in defining specific subsets of CFS patients, and in therapeutic trials. The levels of NPY in the plasma of CFS patients and controls will be compared. The project will also explore the possible relationship of NPY to immune dysfunction in CFS by examining NPY and its regulator, a cell surface enzyme referred to as CD26 that is found in natural killer cells, a special type of immune cell. The levels and activities of NPY and CD26 will be correlated to the clinical severity of CFS.

Role of Mast Cells in CFS Pathogenesis

Mast cells have long been recognized as effectors of the allergic response. More recently this class of immune cells has emerged as a major regulator of neuroimmune and endocrine responses to stress and has been implicated in several stress-related disorders associated with CFS. One project will investigate the effects of different classes of antidepressants on the secretion of various inflammatory molecules that may contribute to the pathogenesis of CFS using cultured human mast cell line activated by the stress hormone, corticotropin-releasing hormone. The basis for the study is preliminary evidence that a tricyclic antidepressant helpful in the treatment of CFS inhibits rat mast cell secretion and intracellular calcium ion levels. The goal of the project is to develop in vitro and in vivo models of CFS and provide supporting data for clinical trials with selected antidepressants.

Alcohol Pharmacogenetics in Mexican Americans

Approximately two-thirds of the U.S. Hispanic population is of Mexican origin. This group suffers from higher rates of alcohol-related problems when compared with individuals from other ethnic backgrounds, which suggests a role for genetic mechanisms. To date, this project has identified unique genetic patterns (polymorphisms) in enzymes involved in metabolizing alcohol in this population. Data from a cohort of Mexican American women with alcohol problems will also be analyzed. Results from the study should provide a better understanding of alcohol use and abuse among this fast growing

segment of American society as well as providing new knowledge regarding ethnic differences in alcohol pharmacogenetics. This project was co-funded by the ORWH as a REAP award.

Initiatives

Request for Applications (RFAs)

- **Neuroimmune Mechanisms and Chronic Fatigue Syndrome**
  The NIAAA participated in this ORWH initiative. The objective was to elucidate the interactions of neural and immune systems in the CFS disease process and to determine how alterations in physiological systems affect the progression and manifestation of CFS. The NIAAA encouraged research that examined co-morbidity between alcohol-related conditions and CFS. Two grants were co-funded by the ORWH and the NIAAA as described above in the section on CFS. (RFA-OD-06-002)

Program Announcements (PAs)

- **Chronic Fatigue Syndrome: Pathophysiology and Treatment**
  The NIAAA participated in this ORWH initiative. The objective was to encourage research on the epidemiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the life span. Major focus areas included understanding of the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mediators influencing multiple body systems that are affected in CFS. (PA-05-030)

Conferences and Workshops

- **National Conference on Women, Addiction, and Recovery: News You Can Use**
  Co-sponsored by the NIAAA, NIDA, and SAMHSA, this conference was designed to advance the field of women's substance abuse treatment by presenting the latest research and discussing how it can be applied and implemented to improve clinical practice and service delivery for women with substance use disorders. Some sessions focused specifically on adolescent girls and minority women.

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 is 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 on fully characterizing the effects of CMV on 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 CMV 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 2005, the NIDCD awarded a contract titled 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 contract are to: (1) correlate CMV status at birth with the presence of permanent/progressive SNHL; (2) acquire data on the incidence, time course, and audiologic outcomes of CMV-related hearing loss; and (3) 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 screening. The necessary milestones have been achieved in Phase I. The study has now progressed to Phase II, which involves pilot testing all aspects of the project before full implementation.

Taste Perception

There are genetic and pathological variations in taste quality perception that affect the intensity of bitter foods and the preference for sweet and fat foods. These perceptions and preferences 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 women with multiple sclerosis and will determine the relationship among 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 ensure 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.

Stuttering

Stuttering is a speech disorder in which sounds, syllables, or words are repeated or prolonged, disrupting the flow of speech. These disruptions may be accompanied by struggling behaviors, such as rapid eye blinks or tremors of the lips. Stuttering can make it difficult to communicate with other people. Boys are twice as likely to stutter as girls. Whereas stuttering is not a condition that is life-threatening, it is a disorder that is life-altering.

In March 2005, the NIDCD sponsored a State-of- the-Science Conference on Developmental Stuttering. The meeting was co-sponsored by the American Institute for Stuttering Treatment and Professional Training, the

National Stuttering Association, and the Stuttering Foundation of America. NIDCD-supported research was presented and highlighted the recent findings supporting the existence of genetic component with significant sex effects.

Assessment and Treatment of Voice Disorders

Voice disorders affect millions of Americans, influencing the quality of their 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 is 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 composed of women.

In June 2005, the NIDCD co-sponsored a research planning workshop with the NINDS, the NIH ORD, and others on spasmodic dysphonia (SD). SD is a rare voice disorder that usually develops spontaneously in midlife. Patients with SD have a hard time speaking; their speech may be strained or choked or alternatively breathy. Patients all report that it requires a huge amount of effort to speak. After the initial onset, the disorder gradually progresses and then remains chronic for life. More women than men are affected; between 60 and 80 percent are female. 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 on function and enhance quality of life.

Initiatives

A number of funding opportunity announcements have been released in the areas of tinnitus, translational research, patient-oriented research, and stuttering, among others.

NATIONAL INSTITUTE ON DRUG ABUSE

As the foremost authority on drug abuse and addiction and sponsor of the vast majority of the world's research on the subject, the National Institute on Drug Abuse (NIDA) addresses the most fundamental and essential questions about drug abuse. The Institute does this by monitoring emerging trends, identifying and studying underlying physiological and social factors, and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within this science is a major effort to investigate issues specific to women and to study sex/gender differences.

NIDA-supported research underscores the complexity of the relationship between drug use and sex/gender and biological vulnerability. Growing evidence suggests that drug abuse may begin and progress differently in women than men; it is characterized by different risk and protective factors and motivations and has different consequences. In recognition of the important role that sex/gender plays in drug abuse, the NIDA has strongly supported research to identify sex/gender differences and specific sex/gender aspects of drug abuse and addiction—applying these findings to design, test, and implement more effective drug abuse prevention and treatment services for both males and females.

The NIDA supports a range of research and activities related to women. For example, the NIDA Women and Gender Research Coordinator and Deputy Coordinator, along with the NIDA Women and Gender Research Group, lead the efforts at the Institute to promote research on issues specific to women and substance abuse. This group has representation from all of the NIDA divisions and offices, covering topics from genetics and basic biology to risk factors, prevention, consequences, and treatment of substance abuse. The major goal of this effort is to infuse the study of sex/gender differences and female-specific issues in all areas of drug abuse research and to disseminate findings.

The current knowledge base for understanding individual characteristics of male and female drug use and addiction is not equal.

Historically excluded from substance abuse studies until the 1990s due to their childbearing potential and to methodological issues associated with the menstrual cycle, women have not realized the benefits of some research findings affecting both treatment and prevention of drug abuse. Since 1994, when the NIH published guidelines on including women and minorities as clinical research subjects, the number of reports being published on substance abuse treatment for women has increased annually. However, more research is needed, not only to stratify results based on gender, but to include gender as a fundamental consideration in the design of studies and interventions aimed at preventing and treating drug abuse.

Accomplishments

The NIDA takes a multipronged approach to improve our understanding of the relationship between sex/gender and drug abuse and addiction. This interest in the impact of drug abuse and addiction on women's health is reflected in research on biological (e.g., hormonal effects) and environmental (e.g., social influences) factors, as well as research on the influence of comorbid disorders (e.g., depression), prenatal effects of drugs, and the differential impact of HIV/AIDS on women. NIDA-supported research in animals serves as a proxy measure for humans and has been used to tease apart some of the biological variables that affect sensitivity to drugs and may contribute to differences seen in males and females with respect to drug exposure consequences. The Institute's clinical and epidemiological studies examine how the presence of other health conditions, along with environmental and social factors, can lead to different patterns of drug abuse and health vulnerabilities between the sexes.

The NIDA also produces publications that summarize important research findings. During FY 2005 and 2006, NIDA published three important documents. The report, Successfully Including Women in Clinical Trials, was published in 2005. It was prepared to assist in the recruitment and retention of women in NIDA's Clinical Trial Network. The report, Mini-Program: Focus on Women and Sex/Gender Differences, was published in 2005 and 2006. This report has been prepared for the College on Problems of Drug Dependence (CPDD) annual conference since 1999. Excerpted from the CPPD program book, this mini-program contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women and Gender Junior Investigator Travel Awardees, announcement of the travel award program for following year CPDD meeting, and information on current NIDA funding opportunities relative to women and sex/gender differences. The report, A Collection of NIDA Notes: Articles That Address Women and Gender Differences Research, was published in 1996, 1997, 1999, 2002, 2004, and 2006. It is a compilation of research articles from the NIDA Notes newsletter. Originally published in 1996, it is revised periodically, most recently in October 2006.

The accomplishments that follow reflect the Institute's comprehensive approach to understanding and using multiple internal and external factors that vary by gender to develop targeted prevention and treatment programs.

Greater Biological Vulnerability for Females

Although more research is needed, both animal models and clinical studies strongly suggest that biological factors underlie many of the differential responses of females to drug effects. Biological differences can be found in genetics, sex hormones, and even the male and female brains, as imaging studies are beginning to show. Biological differences may also account for the fact that even with fewer years of substance use, females at treatment entry average more medical, psychiatric, and adverse social consequences of their substance use disorders than males. Summaries of select research findings suggesting heightened vulnerability for females are provided below.

Females Exhibit a More Rapid Onset for Cocaine Addiction Than Males

Several animal studies have shown greater sensitivity in females than males to cocaine, as seen in a variety of outcomes. More females than males acquire self-administration and acquire it more quickly. They also exhibit greater motivation for cocaine, greater disrup-

tion in daily control over cocaine intake, and greater cocaine-primed reinstatement of drug-seeking behavior. In a study that analyzed epidemiological data from the National Survey on Drug Use and Health, researchers found that women were three to four times more likely than men to become addicted to cocaine within 24 months of the first time they used it. Similarly, in a separate clinical study, while objective medical tests showed no difference in the response of males and females to cocaine or cocaine mixed with alcohol, in self-reports, females consistently reported higher rates of "feeling good" than men. (Lynch, W. *Experimental and Clinical Psychopharmacology*, 14:34-41, 2006; O'Brien, M.S. and Anthony, J.C. *Neuropsychopharmacology* 30:1006-1018, 2005; McCance-Katz, E.F., et al. *Substance Use and Misuse* 40:511-528, 2005)

Following Nicotine Exposure, Adolescent Females Become Addicted More Rapidly Than Males

One study found that adolescent females between the ages of 12 and 13 years developed tobacco dependence symptoms faster than their male counterparts. These symptoms included failed quit attempts and reports of strong cigarette cravings. Women's dependence symptoms occurred at three weeks from onset of monthly use vs. six months for males. The number of symptoms of nicotine dependence in monthly users of nicotine was also significantly higher for females than males, suggesting that it may be more difficult for female adolescents to quit smoking. (DiFranza, J.R., et al. *Tobacco Control* 11:228-235, 2002)

Environmental/Social Influences on Female Drug Abuse

Along with biological variables, social variables and environmental influences also play key roles in women's vulnerability to, as well as their protection from, drug abuse. This may reflect the strong social networks that females tend to form. Historically, males appear to use and abuse drugs at a much greater rate than females, but recent trends indicate that young girls are catching up with boys in their abuse of many drugs (with the exception of marijuana). This may indicate increased opportunities for girls to use drugs or changes in the social milieu that make this behavior more acceptable. Regardless of the reason, these findings portend problems for the future. This trend is especially apparent among young girls 12- to 17-years-old. These findings have important prevention implications for targeting early risk factors associated with drug use. Research highlights on environmental and social influences on drug use and abuse follow.

Motivations to Abuse Prescription Drugs Differ in Females and Males

While young men and women abuse prescription drugs for several of the same reasons, women are more likely to do so for their intended effects (e.g., stimulants to increase alertness). Men are more likely to report that they abuse the drugs to get high. In the case of prescription stimulants, such as Adderall and Ritalin, which are both prescribed for attention deficit hyperactivity disorder (ADHD), college-age women were more likely to attribute their non-medical use to attempts to improve academic performance and to lose weight. College-age men more often reported using these drugs to experiment and to counteract the effects of other drugs. College-age men were also about twice as likely to abuse pain medications (i.e., opioids, such as Vicodin, OxyContin, Tylenol 3 w/codeine, Percocet, Darvocet, morphine, hydrocodone, oxycodone) to get high or for experimentation. These male-female differences call for targeted education strategies. (Teter, C.J., et al. *Pharmacotherapy* 26:1501-1510, 2006; McCabe, S.E., et al. *Addictive Behaviors* 32:562-575, 2006)

Relationships with Family or Significant Other Play Influential Roles in Women Starting, Continuing, and Recovering from Drug Abuse

Psychosocial studies suggest strong roles for different types of social norms on male vs. female adolescent substance use. One study looking at this relationship among seventh graders found that boys were more likely than girls to use marijuana if they perceived that more of their peers used substances. Similar perceptions contributed to greater alcohol use for girls. The study calls for prevention researchers to target norms-based messages to one gender or another or to particular drugs or ethnic/racial groups, given the important

moderating effects of these factors. (Elek, E., et al. *Journal of Drug Issues* 36:147-171, 2006)

Comorbid Mental Illness: Differential Associations in Men and Women

To further understand the complex set of risk factors that set the stage for drug abuse, NIDA researchers have explored the influence of co-occurring psychiatric disorders. Comorbidity can be important because it may point to a risk factor for or a consequence of drug abuse. In both cases, there is evidence of male-female differences in comorbid mental illnesses. For example, a recent longitudinal study examining the onset of adolescent psychiatric disorders found a progression from anxiety to a substance use disorder was significantly more likely to occur in female than in male adolescents. A different pattern was seen in recent NIDA-supported study that used data from about 19,000 teens. These analyses showed that girls and boys exhibiting high levels of risky behaviors (e.g., drugs, sex, and alcohol) were at risk—and equally so—for developing symptoms of depression. However, gender differences occurred with low and moderate levels of risky behaviors. The risk for depressive symptoms was increased two- to three-fold for girls, but it was not increased for boys. Depression did not increase the likelihood of risky behaviors in either girls or boys. This area warrants additional research to help us better understand the differential comorbidity trajectories in males and females. Other selected research findings in this area are summarized below. (Sung, M., et al. *Drug and Alcohol Dependence* 75:287-299, 2004; Hallfors, D.D., et al. *American Journal of Preventive Medicine* 29:163-170, 2005)

Girls and Women Are More Likely to Experience Anxiety, Trauma, and Victimization, Risk Factors for Substance Abuse

Estimates suggest that the majority of women seeking treatment for drug abuse report lifetime histories of sexual and/or physical assault. Childhood abuse and victimization from partners also increase the likelihood that women will experience symptoms of depressive posttraumatic stress. Depressive posttraumatic stress is more prevalent among females than males with substance abuse problems. A history of physical abuse by a known person (not a stranger) is also independently associated with drug treatment initiation. Trauma can be diverse in its effects, as highlighted in a recent longitudinal analysis showing that women who lived in shelters or experienced major violence had a two-fold increase in their risk of depression over a six-month followup. NIDA clinical trials continue to test new treatments for women with co-occurring trauma and substance use disorders. The Institute also supports studies seeking to add a violence prevention component to substance abuse treatment for male perpetrators of intimate partner violence. In addition, research on cohabitating substance-abusing patients is offering options to treatment providers who work with partner-violent couples, 40 to 60 percent of whom reported episodes of partner aggression in the year preceding treatment entry. (Swan, S.C., et al. *Violence and Victims* 20:267-285, 2005; Back, S.E., et al. *Journal of Substance Abuse Treatment* 29:29-37, 2005; Najavits, L.M., et al. *American Journal of Psychiatry* 155:214-219, 1998; Kessler, R., et al. *Archives of General Psychiatry* 52:1048-1060, 1995; Walton-Moss, B. and McCaul, M.E., *Addictive Behaviors* 31:246-253, 2006; Rayburn, N.R., et al. *Journal of Consulting and Clinical Psychology* 73:447-677, 2005; Fals-Stewart, W. and Kennedy, C. *Journal of Substance Abuse Treatment* 29:5-17, 2005)

Males and Females Exhibit Different Patterns of Comorbidity

In general, females are approximately twice as likely as males to experience mood or anxiety disorders. However, males are much more likely to be diagnosed with ADHD, antisocial personality disorder, and oppositional defiant disorder (ODD), a condition characterized by defiance and outbursts of temper. Girls more often than boys tend to experience internalizing disorders, such as depression and anxiety. The gender-associated differences in these disorders may make girls less likely to come to the attention of caregivers and school personnel than boys with harder-to-miss externalizing disorders. Therefore, girls with co-occurring depression and substance abuse problems may not receive treatment for either condition. The Great Smoky Mountain Study analyzed longitudinal data from 1,420 participants to exam-

ine the effects of age at first substance use and the influence on psychiatric comorbidity and other environmental factors on development of substance use disorders (SUD) in adolescents. This study found that boys, but not girls, with a history of depression were at increased risk of having an SUD. Anxiety increased SUD risk in girls between the ages of 13 and 16, as did conduct disorder, which is generally more prevalent in boys than girls, for girls older than 14. Thus, in this study, boys with depression and girls with conduct disorder and anxiety were at high risk for SUD. These findings give the traditional internalizing-externalizing story a modified gender switch. The depression drug abuse link in boys and the conduct disorder-drug abuse link in girls are important for targeting prevention efforts. (Sung, M., et al. *Drug and Alcohol Dependence* 75:287-299, 2004)

More Girls Than Boys Have Late Onset Antisocial Behavior, A Risk Factor for Substance Abuse

Antisocial behaviors are usually first seen in young children and do not typically emerge during the adolescent years. One study compared late onset antisocial behavior (beginning in mid- to late-adolescence) with more commonly recognized courses of antisocial behavior (i.e., persisting or beginning by early adolescence and continuing through late adolescence; and desisting and stopping by mid-adolescence). Investigators found females to be overrepresented in the more unconventional late onset group. Although typically overlooked, late onset antisocial behavior is associated with clinically significant problems in young people who have it, including elevated risk for subsequent nicotine, alcohol, and cannabis dependence. The comparison in this study showed that youth with late onset and those with persisting antisocial behavior were both at increased risk of substance abuse problems. The late onset group also included a significant overrepresentation of females, while the persisting and desisting groups included more males. Prevention implications from these findings include the need for clinicians, parents, and teachers to recognize this pathway, particularly for vulnerable young women, even if they do not meet the conventional criteria used to diagnose antisocial personality disorder. (Marmorstein, N.R. and Iocono, W.B. Journal of the *American Academy of Child and Adolescent Psychiatry* 44:1284-1291, 2005)

Prenatal Exposures to Drugs: Effects on Future Behavior Patterns in Male and Female Offspring

Despite the well-established dangers of using licit and illicit drugs during pregnancy, pregnant women continue to abuse substances that cross the placenta and negatively impact the fetus. Latest National Survey on Drug Use and Health data reveal that among pregnant women between the ages of 15 and 44 years, 3.9 percent reported using illicit drugs in the past month. This rate was significantly lower than the rate among women age 15 to 44 who were not pregnant (9.9 percent). The CDC reported that more than 10 percent of women giving birth in 2003 were cigarette smokers, with about one-quarter smoking half a pack or more per day and the highest rates occurring among women 18 to 24 years old. Although the past decade has witnessed declines in smoking during pregnancy, continued abuse of legal and illegal drugs during pregnancy calls for vigilant and sustained prevention efforts. The following are highlights of some recently published NIDA-supported research findings on the relationships between prenatal exposure to drugs and developmental behavior patterns, some of which show gender differences. Ongoing research is continuing to identify specific and often subtle differences in development between exposed and non-exposed children. Research is also striving to increase our understanding of the mechanisms underlying the differences that occur. This is complex and challenging work, in large part because of the many confounding factors, including parenting quality, polydrug use, socioeconomic status, and exposure to stress and violence. (U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *National Survey on Drug Use and Health*, 2006)

Prenatal Exposure to Tobacco Alters Behavior as Children Develop

Recent studies show a link between prenatal tobacco smoking and disruptive behavior in early development. A study of prenatal smok-

ing and the early emergence of disruptive behavior disorders showed exposed toddlers to be at increased risk of early-starter pathway to conduct problems. While the study's exploration of sex differences was preliminary in light of the small sample size, there was no evidence that patterns of early disruptive behavior were restricted to boys. In light of other study findings, there seems to be no support for the notion that girls are "immune" to the adverse effects of prenatal exposure to cigarettes, at least in the first years of life. While not necessarily proving a causal relationship, these findings suggest that particular areas of the brain may be affected by prenatal tobacco exposure and highlight a potential window of opportunity for early interventions aimed at altering disruptive behavior pathways before they become serious clinical patterns. More studies with sample sizes sufficient to examine separate trajectories for boys and girls are needed to better understand how and when exposure may heighten each gender's risk for antisocial behaviors. (Wakschlag, L.S., et al. *Child Development* 77:893-906, 2006)

Research Shows Apparent Gender-specific Effects Associated with Prenatal Cocaine Exposure

A recent study examining childhood aggression in five-year-olds suggests that boys exposed to high environmental risk (e.g., chaotic home environment, poverty) were more likely than girls to show continued aggression over time. Although for nearly all aggression measures, cocaine-exposed children (boys and girls) were rated by parents and teachers as more aggressive than those who were not exposed. Moreover, boys were rated as more aggressive on every measure than were girls. In another report from an ongoing longitudinal study of child development following prenatal cocaine exposure, language functioning at six and 9.5 years was found to be different in boys and girls. Specifically, children at six years had lower expressive language if they were female. Researchers continue to study these and other linkages between prenatal drug exposure and offspring outcomes and to identify significant male-female differences. (Bendersky, M., et al. Journal of Pediatric Psychology 31:71-84, 2006; Beeghly, M., et al. *Journal of Pediatric Psychology* 31:98-115,2006))

Prevention and Treatment Approaches: One Size Does Not Fit All

A major reason for understanding male-female differences in the constellation of contributory factors to drug abuse is to develop more effective prevention and treatment programs. The biological differences and social/environmental factors discussed above have potential prevention and treatment implications, influencing how and when to intervene, the reasons and settings for seeking treatment, the prevention messages and treatments that are most effective, and the consequences of not receiving treatment. Understanding gender differences can help inform the tailoring of prevention and treatment approaches and increase the likelihood of positive outcomes.

Examples of successful NIDA-supported gender-based prevention programs include those targeting male and female high school athletes. The programs are known as Athletes Training and Learning to Avoid Steroids (ATLAS) for boys and Athletes Targeting Healthy Exercise and Nutrition Alternatives (ATHENA) for girls. ATHENA addresses a constellation of risk behaviors, ranging from disordered eating habits to drug use to safe driving. Recent results from ATHENA show that girls taking part in the program were less likely to use diet pills or performance-enhancing substances and also made positive changes in strength training, perceptions of self efficacy, and healthy eating behaviors. As noted earlier, since girls are more likely to abuse prescription medications to improve performance and body image, ATHENA is skillfully adapted to address these motivations. Other select research highlighting gender-related findings with prevention and treatment implications are summarized below.

Programs that Include Gender-Sensitive Strategies Stand to Achieve Optimal Outcomes for Both Males and Females

The NIDA supported a study comparing the effects of a broad-based vs. targeted prevention program on high-risk behaviors among African American youth in the fifth and sixth grades. Data from this study provide strong evidence that outcomes can differ by gender. The study addressed multiple problematic behaviors via

a single intervention. The investigators found significant reductions in multiple health indicators, including drug abuse, violence, provocative behavior, and sexual behaviors for boys. Unfortunately, no reductions were seen for girls. In contrast, a study evaluating the efficacy of a standard life skills training curriculum with rural youth showed reductions in alcohol use, marijuana use, and binge drinking only in females, with no effect seen in males. Together, these studies demonstrate the value of incorporating gender analysis; if either study had not done so, the positive outcomes, albeit for one sex, might not have been detected. Gender differences underlying positive outcomes not only have significant implications for allocating prevention resources, they also affirm the need to customize programs to achieve optimal effectiveness for both males and females. (Flay, B.R., et al. *Archives of Pediatric and Adolescent Medicine* 158:377-384, 2004; Vicary, J.R., et al. *Health Education and Behavior* 33:325-339, 2006)

Women Are Underrepresented among Individuals Seeking Drug Abuse Treatment

Women are underrepresented among those seeking treatment for drug abuse even when their lower prevalence rate of drug abuse is taken into account. This disparity may stem from a constellation of cultural, economic, and health factors that could include stigma, lack of family support, need for child care, pregnancy, fears concerning child custody, comorbid psychiatric problems, and treatment access. In addition, women and men define their substance-related problems differently, bringing them to different health care settings and potentially contributing to different rates of substance abuse treatment entry. In general, it appears that females with substance use disorders are less likely than males to use substance abuse services and are more likely to seek medical care in general or mental health sectors. By visiting doctors or other health care professionals who do not specialize in drug treatment, women may receive a diagnosis of psychiatric or other conditions, appropriately or not, but not one of drug addiction for which treatment is also needed. It is therefore important to screen for substance abuse in health care settings used by women. In addition, the fact that many more men than women are referred to drug rehabilitation programs by the criminal justice system suggests that treatment setting differences may have less to do with gender preference than larger societal issues. However, regardless of why men and women receive services from different treatment settings, the fact that they do may help explain some of the gender disparities in treatment entry and in ever receiving treatment. (Greenfield, S., et al. *Drug and Alcohol Dependence* 86:1-21, 2006)

Pharmacologic Benefits of Specific Drugs May Extend Preferentially to One Sex

Because many of the medications currently on the market were tested in men, it was not generally known whether the results from those studies are applicable to women or whether differences would emerge when used in women. Recent studies are showing that medications that work in males do not necessarily work as well in females. For example, disulfiram, a drug approved for alcoholism, was recently shown to be efficacious in treating cocaine addiction as well, but only in men. In addition, studies show that males appear to respond more favorably to nicotine replacement therapy (NRT) than females. A meta-analysis of nicotine replacement therapies (NRTs) showed them to be more effective in men than in women at three- and six-month followup; by 12 months, they were effective only in men. Perhaps this outcome is partially explained by another research finding: nicotine metabolism is faster in women than men. This is important because faster nicotine metabolizers have poorer smoking cessation outcomes when using transdermal NRT. These findings suggest that the differences in smoking rates and behaviors in females (who are generally less successful in quitting) stem from an interplay of cultural and biological differences. This provides an interesting starting point for devising gender-specific interventions. (Nich, C., et al. *Addictive Behaviors* 29:1123-1128, 2004; Cepeda-Benito, A., et al. *Journal of Consulting and Clinical Psychology* 72:712-722, 2004; Benowitz, N.L., et al. *Clinical Pharmacology and Therapeutics* 79:480-488, 2006; Lerman, C., et al. *Clinical Pharmacology and Therapeutics* 79:600-608, 2006)

The Menstrual/Estrous Cycle as a Determinant of Drug Action

In animals, many behavioral effects of drugs are influenced by the estrous cycle. Investigators can eliminate cycle-associated effects by ovariectomy and subsequent administration of estradiol. Suggestive evidence from both animal and human studies indicates that progesterone may also play a role in cocaine's subjective effects and may contribute to gender differences in cocaine sensitivity. In one study in humans, administering progesterone to females during their follicular phase lessened positive subjective effects of smoked cocaine. However, administering progesterone to males did not alter subjective effects. This result suggests possible therapeutic application of progesterone in females. In another study, women reported lower ratings of feeling high on cocaine during the luteal phase than did women in the follicular phase; they also reported lower rates of feeling high than men. This may mean that ovulating women are more vulnerable to cocaine relapse during the follicular phase when progesterone levels are lower. This finding could have important treatment implications. A recent NIMH-supported study also showed that during the follicular phase, when estrogen is unopposed by progesterone, women may be more apt to use drugs, have sex, or engage in pleasurable activities. (Evans, S.M., et al. *Neuropsychopharmacology* 31:659-674, 2006; Sofuoglu, M., et al. *Experimental and Clinical Psychopharmacology* 7:274-283, 1999;Sofuogluy, M., et al. *Pharmacology, Biochemistry, and Behavior* 78:699-705, 2004; Dreher, J.C., et al. *Proceedings of the National Academy of Sciences of the United States of America* 104:2465-2470, 2007)

Treatments that Focus on Trauma and Drug Abuse Can Be Effective

Early stresses, such as child sexual abuse, are more common in girls than in boys. They are also associated with a risk of substance abuse problems, as are other forms of traumatic victimization, including exposure to violence in adulthood. Significant associations between PTSD, marked by childhood sexual abuse, and substance use disorders among women have made trauma a key assessment factor when treating substance-abusing women. To address this issue, the NIDA is supporting clinical trials to help dually diagnosed women meet their treatment goals through a promising trauma-focused cognitive behavioral therapy (CBT) known as Seeking Safety, which was designed specifically for women with trauma. The NIDA Clinical Trials Network is testing the findings of a study showing that Seeking Safety can improve both substance abuse and PTSD symptoms compared with standard substance abuse treatment. In the earlier study, female patients identified trauma's effects on their lives, including substance abuse, and practiced techniques to ease emotional pain, stop self-blame, and cope with difficult interpersonal and potential relapse situations. Another study highlighted the value of screening for violence exposure among substance-abusing pregnant women, who are at particularly high risk and who need specific therapeutic strategies to help them address a complex array of problems. (Kendler, K.S., et al. *Archives of General Psychiatry* 57:953-959, 2000; Najavits, L.M., et al. *American Journal on Addictions* 6:273-283, 1997; Cottler, L.B., et al. *American Journal of Psychiatry* 149:664-670, 1992; Hien, D.A., et al. *American Journal of Psychiatry* 161:1426-1432, 2004; Velez, M.L., et al. *Journal of Substance Abuse Treatment* 30:31-38, 2006)

Findings that gender often plays a role in treatment has prompted the NIDA to call on clinicians and researchers to: (1) jointly address common and unique predictors of treatment outcomes for subgroups of women and men; and (2) devise strategies targeted at program characteristics that are differentially associated with positive outcomes in both genders. We must become better at determining which treatment and treatment services approaches need to be tailored to address those unique consequences associated with drug use experienced by each sex.

One environment in which limited access to treatment may unfairly affect women in particular is the criminal justice system. As the number of women with drug addiction has soared over the past few decades, so has the female prison population. Latest data show that among federal female inmates, drug use in the month before the offense occurred rose sharply. The rate increased from 37 percent in 1997 to 48 percent in 2004, in increase of 11 percent. Unfortunately, few addiction treatment programs are designed to meet women's

specific needs, especially a history of physical or sexual abuse and multiple comorbid psychiatric disorders. Data confirm that female inmates in state and federal prisons have markedly higher rates of mental health problems than male inmates (73 percent of females vs. 55 percent of males in state prisons; 61 percent of females vs. 44 percent of males in federal prisons). Findings from NIDA-supported criminal justice research studies show substantial differences in background characteristics for men and women, while also calling for more research on gender-specific paths of recovery to understand the degree to which these differences affect treatment and post-treatment needs and outcomes. (Bureau of Justice Statistics Special Report, *Drug Use and Dependency, State and Federal Prisoners*, 2004. October, 2006; Bureau of Justice Statistics Special Report, *Mental Health Problems of Prison and Jail Inmates*. September 2006; Messina, N., et al. *American Journal of Drug and Alcohol Abuse* 32:7-28, 2006)

Following release from incarceration, both men and women benefit from participating in community-based aftercare treatment, which greatly reduces the likelihood of drug and crime recidivism. The provision of comprehensive services, such as education, housing, and income support also yield improved treatment outcomes for men and women. In addition, services that respond to gender-specific needs, such as child-care services for women, may further enhance treatment outcomes. More clinical trial research is needed that addresses issues of gender-specific treatment and treatment services, both during and after incarceration, to determine more clearly what works and what does not.

HIV/AIDS: Changing Risks for Women

For both males and females, few drug abuse consequences are more severe than HIV infection. Drug abuse heightens the risk of contracting HIV through shared injection equipment and altered decisionmaking, resulting in increased sexual risk-taking behaviors. While all groups are affected by HIV/AIDS, not all are affected equally. African Americans experience striking disparities in HIV infection rates compared with other populations. While they make up just 13 percent of the U.S. population, African Americans accounted for more than half of the total AIDS cases diagnosed in 2004. Moreover, African American females accounted for 68 percent of the female HIV/AIDS diagnoses from 2001 through 2004 while white females accounted for 16 percent and Hispanic females for 15 percent. (CDC. *Morbidity and Mortality Weekly Report* 53:1106-1110, 2004)

Recent epidemiological research indicates that non-drug abusing women are contracting HIV at an alarming rate through sexual contact with HIV-positive males. The CDC reports that, of all new HIV/AIDS diagnoses in women, 54 percent were in African American women infected through heterosexual contact. To address these trends, the NIDA supports a comprehensive HIV/AIDS research portfolio covering gender-related differences in factors that contribute to and protect from HIV risk. Other studies are identifying gender-specific strategies to decrease injection drug use and high-risk sexual behaviors among women and men. Highlights of selected research findings are summarized below and demonstrate the importance of assessing HIV prevention and treatment interventions separately by gender. (CDC. *Morbidity and Mortality Weekly Report* 55:585-589, 2006)

Men and Women Display Different Injection Drug Use Patterns

Indepth interviews with male and female injection drug users in two U.S.-Mexico border cities revealed that men buy and inject with strangers in shooting galleries. However, women buy and inject with known/trusted friends. This finding suggests a need for venue-based interventions for men and personal network interventions for women. (Cruz, M.F., et al. *AIDS and Behavior* 11:253-262, 2007)
Counseling and Risk-reduction Intervention Is Effective in HIV-positive Women

A recent study found that, following HIV testing, counseling and a risk-reduction intervention, HIV-positive women were nearly two and a half times more likely than HIV-negative women to have entered residential treatment for drug abuse. HIV-positive women were also approximately twice as likely to have decreased their number of sex partners, frequency of unprotected sex, and level of alcohol and crack

use. These outcomes demonstrate the effectiveness and importance of interventions for HIV-positive women. (Inciardi, J.A., et al. *AIDS Care* 17S:S88-S101, 2005)

Women-focused HIV Intervention Is Effective among Sex Workers in Pretoria, South Africa

A study comparing the effectiveness of a women-focused HIV intervention with a standard HIV intervention found that women receiving the former had larger decreases in their daily cocaine and alcohol use than those receiving the standard intervention. The women-focused HIV prevention intervention was designed in the U.S. and adapted and implemented in South African sex workers who also reported recent substance use. Although violence continued to be a problem for these women, participants in the women-focused intervention reported at followup that they were victimized less often than women receiving the standard intervention. This study demonstrates the feasibility of implementing cross-cultural behavioral HIV prevention interventions and supports the need for future studies of women's contextual issues and the effectiveness of targeted interventions. (Wechsberg, W.M., et al. *AIDS and Behaviors* 10:131-137, 2006)

Gender Differences Can Predict Condom Use

In a recent study of condom use among incarcerated juvenile offenders, females reported significantly greater knowledge of condom efficacy, less peer influence, higher perceived risk for infection, more positive condom attitudes, and more self-efficacy than males. Nevertheless, they reported less condom use than males. Power imbalances or other dynamics operating in their relationships may make it more difficult for females to use condoms consistently despite knowing their efficacy. Such dynamics operating between young men and women require further exploration because of the implications for a range of risk behaviors—from starting and continuing substance abuse to using condoms consistently to seeking and continuing drug abuse treatment.

Preliminary Findings on Differences Regarding Treatment of HIV-positive Women with Highly Active Antiretroviral Therapy (HAART)

A study of HIV-positive patients on methadone found that women reported more medical side effects of HAART treatment, a higher severity of psychiatric problems, and lower health-related quality of life than men. Women also tested positive for opioids at higher rates than men. Men were more likely to be positive for benzodiazepines. In another study, HAART was also shown to be less effective for women who smoke, pointing to the critical need to promote smoking cessation in HIV-positive women. (Haug, N.A. et al. AIDS Care 17:1022-1029, 2005; Feldman, J.G., et al. *American Journal of Public Health* 96:1060-1065, 2006)

Initiatives

The NIDA seeks to promote research on sex/gender differences and issues specific to women by using a variety of strategies, some of which are listed below. These include the issuance of program announcements (PAs) and requests for applications (RFAs), sponsorship of symposia and meetings, travel awards, keynote and invited addresses, and publications. The following are RFAs and PAs issued by the NIDA in FY 2005 and 2006 that seek to promote research on sex/gender differences and issues specific to females. The list also includes RFAs and PAs that the NIDA co-sponsored with other NIH ICs that seek to promote research on sex/gender differences and issues specific to females.

Request for Applications (RFAs)

- **Developmental Centers for Translational Research on the Clinical Neurobiology of Drug Addiction (P20)**
  (RFA-DA-06-006)
- **Prescription Opioid Use and Abuse in the Treatment of Pain (R01, R03, R21, R25)**
  (RFA-DA-06-005)
- **Social Neuroscience**
  (RFA-DA-06-004)

- **Enhancing Practice Improvement in Community-based Care for Prevention and Treatment of Drug Abuse or Co-occurring Drug Abuse and Mental Disorders**
  (RFA-DA-06-001)
- **HIV and Drug Abuse Interventions among Pregnant Drug Abusers in Treatment**
  (RFA-DA-05-008)
- **Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50)**
  (RFA-OD-06-003)
- **Building Interdisciplinary Research Careers in Women's Health (K12)**
  (RFA-OD-06-004)

Program Announcements (PAs)

- **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36)**
  (PAR-06-476)
- **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36)**
  (PAR-06-446)
- **Behavioral Science Track Award for Rapid Transition (B/START) (R03)**
  (PAR-06-300)
- **Health Disparities in HIV/AIDS: Focus on African Americans (R01)**
  (PA-06-069)
- **Drug Abuse as a Cause, Correlate, or Consequence of Criminal Justice Related Health Disparities among African Americans (R01)**
  (PA-06-068)
- **Non-injection Drug Abuse and HIV/AIDS (R01)**
  (PAS-06-054)
- **International Research Collaboration on Drug Addiction (R01)**
  (PA-06-050)
- **Economics of Prevention and Treatment Services for Drug and Alcohol Abuse**
  (PA-05-111)
- **Science Education Drug Abuse Partnership Award**
  (PAR-05-105)
- **Inhalant Abuse: Supporting Broad-based Research Approaches**
  (PA-05-099)
- **Complementary and Alternative Medicine for Substance and Alcohol Related Disorders**
  (PA-05-097)
- **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences**
  (PAR-05-083)
- **Collaborative Multisite Research in Addiction (COMRAD)**
  (PA-05-067)
- **Research on Rural Mental Health and Drug Abuse Disorders (R01)**
  (PA-06-478)
- **Research on the Reduction and Prevention of Suicidality (R01)**
  (PA-06-438)
- **International Research Collaboration—Behavioral, Social Sciences (FIRCA-BSS) (R03)**
  (PAR-06-437)
- **International Research Collaboration—Basic Biomedical (FIRCA-BB) (R03)**
  (PAR-06-436)
- **The Science and Ecology of Early Development (SEED) (R03)**
  (PA-06-345)
- **Women's Mental Health in Pregnancy and the Postpartum Period (R21)**
  (PA-06-377)
- **Health Research with Diverse Populations (R01)**
  (PA-06-218)
- **Parenting Capacities and Health Outcomes in Youths and Adolescents (R21)**
  (PA-06-098)
- **Parenting Capacities and Health Outcomes in Youths and Adolescents (R01)**
  (PA-06-097)
- **AIDS International Training and Research Program**
  (PA-05-140)
- **Brain Disorders in the Developing World: Research Across the Lifespan**
  (PAR-05-100)

- **Global Research Initiative Program, Social Science**
  (PAR-05-082)
- **International Research Collaboration—Behavioral, Social Sciences (FIRCA-BSS)**
  (PAR-05-073)
- **International Research Collaboration—Basic Biomedical (FIRCA-BB)**
  (PAR-05-072)
- **Research on Sleep and Sleep Disorders**
  (PA-05-046)
- **Research on Mind-Body Interactions and Health**
  (PA-05-027)
- **Community Participation in Research**
  (PAR-05-026)
- **Decision Making in Health: Behavior Maintenance**
  (PA-05-016)
- **Co-Occurring Mental Illness, Alcohol and/or Drug Abuse and Medical Conditions**
  (PA-05-007)

Conferences and Workshops

- **Meeting Treatment Needs of Girls and Women with Co-occurring Conditions**
  This symposium was convened at the annual meeting of American Psychological Association on August 18-21, 2005 in Washington, DC.
- **Changing At-risk Behaviors for HIV/AIDS and Drug Abuse in Women**
  This symposium was convened at the annual meeting of the American Psychological Association on August 18-21, 2005 in Washington, DC.
- **Childhood Maltreatment: Social, Behavioral, and Neurobiological Sequelae and Implications for Drug Abuse**
  This symposium was convened on September 19, 2005 in Rockville, MD.
- **Progesterone Effects on Reward: Possible Role in Drug Addiction**
  This symposium was convened at the combined meeting of The Conference on Sex and Gene Expression and The Workshop on Steroid Hormones and Brain Function on March 28-April 1, 2006 in Breckenridge, CO.
- **Women and Gender Junior Investigator Travel Award Program**
  This program provided travel support for junior investigators to attend the annual meeting of the College on Problems of Drug Dependence on June 17-22, 2006 in Scottsdale, AZ. The program has been in operation since 2000 and is designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences.
- **National Conference on Women, Addiction and Recovery: News You Can Use**
  This conference, which was convened on July 12-14, 2006 in Anaheim, CA, was co-sponsored by the NIDA, the NIAAA, and CSAT/SAMHSA, NIDA, and NIAAA. Program information is available online at http://conferences.jbs.biz/womensconference/WOMProgram.pdf
- **Early Career Investigators Poster Session and Social Hour**
  This session was convened at the annual meeting of the American Psychological Association (APA) in New Orleans, LA on August 10-13, 2006. It was co-sponsored by the NIDA, NIAAA, and APA Divisions 28 and 50. Five posters dealt with sex/gender differences in drug abuse.
- **Adolescent Smoking: Gender-Specific Biological, Social, and Psychological Risk Factors**
  This symposium was convened at the annual meeting of the American Psychological Association in New Orleans, LA on August 10-13, 2006.

Health Disparities among Special Populations of Women

The NIDA recognizes that treatment needs for drug abuse and addiction often differ according to a range of variables, including gender, age, co-morbidity status, and ethnic group. Thus, treatment approaches are needed that address special populations, which include subgroups of women, such as those with children or who are pregnant or postpartum, women with drug-using partners, or women experiencing current and past violence and trauma. Other special populations of drug

abusers include criminal offenders, the homeless, those living with or at risk for HIV/AIDS, and members of particular ethnic or minority groups. Ongoing NIDA-supported treatment and services research targets these and other groups because of our belief that continuing research into population-specific treatment needs will ultimately result in a greater number of people seeking treatment and having successful outcomes. This population-specific focus also extends to addressing questions about the extent to which membership in these special populations plays a role in the etiology of drug abuse and whether those individuals have unique drug abuse consequences, and whether they are different for males and females. While recent NIDA-supported research on some of these groups has been described above, additional studies dealing with specific ethnic groups are presented below. These include studies that have examined drug use patterns among particular ethnic minority populations, such as American Indians and African Americans, where striking disparities exist in health and drug abuse and addiction.

Young American Indian Girls at Special Risk of Abusing Certain Drugs

Data analyzed from a 1997 survey of self-reported substance use among a sample of more than 5,800 white and American Indian adolescent seventh graders in a Northern Plains state indicated that rates of lifetime and past-month use of cigarettes and marijuana were higher among American Indians than among whites of the same gender. Also, the rate of lifetime and past-month use of cigarettes and inhalants among American Indian girls exceeded that of American Indian boys as well as white girls and boys. These findings add to the sparse literature on substance use among young adolescents of varying ethnicity and underscore the importance of examining early gender-specific substance use patterns, so as to design more responsive prevention interventions.

Cigarette Smoking in Two American Indian Tribes Finds Uneven Odds for Males

The previously referenced study found seventh-grade females to smoke more than males. Another NIDA-supported study examining the prevalence and correlates of cigarette smoking in two American Indian reservation populations found that older boys smoked more. A cross-sectional regression analysis associated male gender and younger age (population spanning 15 to 54 years of age) with higher odds of smoking in a Southwest tribe, whereas in a Northern Plains population, current or former marriage and less time spent on a reservation correlated with greater smoking odds. Taken together, these studies support the need to identify subgroup differences to avoid overly generalized, one-size intervention solutions. (Henderson, B.E., et al. *American Journal of Public Health* 95:867-872, 2005)

Drug Use Strongly Correlated with Female Suicide Ideation in American Indian Youth

Research examining suicide ideation among American Indian youth (average age of 12 years) in or near reservations in the northern Midwest states revealed that nearly one in 10 had current thoughts of killing themselves. Females were more than twice as likely as males to think about suicide, and drug use was the strongest correlate of suicidal thoughts for both boys and girls. Researchers recommend that suicide prevention programs draw on the strengths of American Indian culture, with particular attention given to young females, drug use, and self-esteem issues. (Yoder, K.A., et al. *Archives of Suicide Research* 10:177-190, 2006)

Nicotine Dependence Associated with Particular Gene Sub-type in African American Females

A study of more than 2,000 European or African American males and females from more than 600 families has found two different single nucleotide polymorphisms (SNPs) (i.e., DNA sequence variations) associated with measures of smoking in each of the two ethnic groups. Each individual has many SNPs that together create a unique DNA pattern for that person. After statistical adjustments, one haplotype or set of closely linked genetic markers remained significant in African American females. SNPs promise to significantly advance our ability to understand and treat human disease by identifying genetic vulnerability, particularly relative to gender and to minor-

ity and subgroup populations. (Li, M.D., et al. *Human Molecular Genetics* 14:1211-1219, 2005)

HIV and Minority Women: Certain Characteristics Distinguish African American Women from Other Ethnic and Cultural Groups

Recent research investigating HIV risk factors for African American women identifies six distinguishing factors: (1) structure of relationships, with African Americans having fewer men-to-women ratios than other groups (i.e., sexual networks are small); (2) cumulative trauma and stress over time; (3) generational poverty; (4) under education and poorer quality schools; (5) health disparities in access, treatment, and acceptability of services (i.e., mistrust); and (6) lack of cultural congruence (i.e., a disconnect between the messenger and the message, which often does not inculcate meaningful cultural values). Other recent research reveals similar factors that serve as barriers to health care for HIV-positive African American women with substance abuse problems and histories of childhood sexual abuse. Such barriers to health care include confidentiality issues, poor financial resources, difficulty getting an appointment, excessive waiting to see a health care provider, and obligation to care for others. Early traumatic experiences, including child sexual abuse, may exacerbate the problems that HIV-positive African American women face. Such findings suggest the need for culturally relevant interventions for HIV and substance abuse prevention, focusing on health resilience and recovery (i.e., teaching women how to re-enter sobriety/recovery phases of their lives). (Wyatt, G., et al. Unpublished data from a study of health, mental health, and drug disparities for African American and Latinas at risk for HIV, 2007; Wyatt, G., et al. *Poor and Underserved* 16:9-23, 2005)

Gender Analysis

The NIDA has emphasized sex/gender analysis research for more than 10 years, and many of the research findings described above result from the Institute's efforts to actively promote the study of sex/gender differences in drug abuse in all areas of research. This research suggests that gender often plays a pivotal role in the etiology, prevention, and treatment of drug abuse and its consequences. Advancing our understanding of these roles is crucial on personal, societal, and economic levels. As anyone who has had a relative or friend with a drug abuse problem knows, it is one that affects more than the individual. Indeed, the personal and societal costs of addiction are great. Drug abuse is inextricably linked to the spread of infectious diseases such as HIV/AIDS, STDs, tuberculosis, and hepatitis C, and it is often implicated in family disintegration, academic failure, loss of employment, psychiatric disorders, cognitive dysfunction, poor health, negative pregnancy outcomes, impaired parenting, domestic violence, and other crimes. Putting dollar figures on these statistics, substance abuse—including smoking, illegal drugs, and alcohol—costs this country more than half a trillion dollars a year, with illicit drug use alone accounting for about $181 billion. For a child with a parent who is addicted to drugs, the cost is incalculable. (Office of National Drug Control Policy. *The Economic Costs of Drug Abuse in the United States*, 1992-2002. Washington, D.C.: Executive Office of the President, 2004)

One-size-fits-all, unisex research approaches are giving way to approaches recognizing the value of taking a sex/gender-based research approach and analyzing data separately for males and females. Indeed, findings from the NIDA's basic, clinical, and epidemiological research studies are increasingly showing sex/gender to be a major determinant of outcome. Research including studies that use gender-blind intervention approaches often yield results that occur only in one gender. Although effective interventions have been developed that do not reflect the research literature on gender differences in drug abuse etiology, research increasingly suggests that gender-sensitive interventions may garner higher rates of success for both males and females. Thus, sex/gender should be an integral consideration in the design of all drug abuse and addiction research, to achieve optimal value from it.

OFFICE OF DIETARY SUPPLEMENTS

The Office of Dietary Supplements (ODS) supports research to expand the evaluation of the role of dietary supplements in disease prevention and the reduction of risk factors associated with disease. In addition, the ODS supports research to further understanding of the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle.

Accomplishments

The ODS supports research on a range of issues related to women's health. Included in the ODS research portfolio are projects on the following disease and conditions that affect women.

- *Breast Cancer:* The role of phytoestrogens and their relationship to inhibiting and/or promoting breast cancer is of high interest to the ODS. The ODS co-funds basic and observational research in this area with the NCI, the NIA, and the NCCAM.
- *Menopause:* The ODS co-funds basic and clinical studies in the area of CAM therapies for women's health and menopausal symptoms with the NCCAM. This includes a Botanical Research Center that is focused on women's health. Botanicals under study include black cohosh, red clover, and soy. The Botanical Research Center is charged with characterizing and standardizing plant extracts to be used in future clinical trials for the evaluation of effect on menopausal symptoms.
- *Reproductive Health:* The ODS co-funds two training grants on conditions affecting unborn children with the NHLBI and the FIC. Through a cooperative agreement, the ODS co-funds an international grant focused on agriculture, maternal-infant nutrition, and public health.

The ODS, in conjunction with ORWH, also sponsors a BIRCWH project at the University of California, Davis.

OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

The Office of Behavioral and Social Sciences Research (OBSSR) opened officially on July 1, 1995. The U.S. Congress established the OBSSR in the Office of the Director (OD), NIH, in recognition of the key role that behavioral and social factors often play in illness and health. The mission of the OBSSR is to stimulate behavioral and social sciences research throughout the NIH and to integrate these areas of research more fully into others of the NIH health research enterprise, thereby improving our understanding, treatment, and prevention of disease.

Given its mission to develop and support projects that generate interest among a range of NIH ICs, the OBSSR does not typically initiate programs that narrowly target specific diseases. The Office, however, does support some individual research projects that have clear relevance to women's health.

Accomplishments

Mind, Body, and Health

Several common chronic disorders, including chronic visceral and somatic pain syndromes, disorders of mood and affect, and addictive behaviors, can be related to alterations in the neurobiology of the central stress system. Some of these disorders, including functional GI disorders, depression, and anxiety, are significantly more common in women and cause considerable morbidity and impairment in quality of life. Moreover, satisfactory, cost-effective treatments are generally not available. The OBSSR is co-funding, with the NCCAM, the UCLA Center for Neurovisceral Sciences and Women's Health (CNS/WH), which has assembled a large number of clinical and basic investigators interested in mind/body interactions. The investigators at this center have a particular interest in the role of stress and sex-based differences in altering these interactions in health and disease. Many of the center's ongoing interdisciplinary and interdepartmental collaborations span a wide range of molecular, behavioral, brain imaging, and health outcomes studies.

Type 2 Diabetes and Coronary Heart Disease

Coronary heart disease (CHD) is the leading cause of death and functional limitations among women in the U.S. Postmenopausal women with diabetes are at especially high risk of CHD, but CHD research with this population is very limited. In collaboration with the NHLBI, the OBSSR is funding research to address the poorly understood natural history of long-term maintenance of change in multiple behaviors (i.e., dietary behaviors, physical activity, and stress management) related to CHD risk. In addition, research is studying the effects of theoretically important mediating variables on relapse and maintenance. This work is a continuation of research that has already demonstrated significant and consistent positive effects of a lifestyle change intervention on reduction of behavioral CHD risk factors in a sample of postmenopausal women with type 2 diabetes. This research relies on a framework that synthesizes social-cognitive, social-ecologic, and goal-systems theories. The Mediterranean Lifestyle Program (MLP), a comprehensive lifestyle change intervention, yielded significant behavioral, psychosocial, and physiologic outcomes at six and 12 months postintervention. In the natural history continuation study, the longer-term (three to seven years) effects of the MLP are being examined using a variety of statistical approaches. In addition, the potential for translating this program into the real world is being assessed using the RE-AIM evaluation framework. In addition, a cost-effectiveness analysis is being conducted. Dissemination of the intervention is planned if it proves cost-effective. This work represents the next logical step in this line of research, as it examines long-term maintenance of behavior change and lays the groundwork for translation of this successful intervention into practice. It will also provide important scientific and theoretical information about the patterns of maintenance and relapse among multiple risk factors and about the relative importance of theoretical mediating variables (e.g., self-efficacy; problem-solving; peer and community support).

Eating, Activity, and Overweight

Adolescence represents a critical period for the development of overweight that tracks into adulthood. This risk is significantly heightened for teens who become pregnant and experience postpartum weight retention. Such weight gain can lead to impaired glucose tolerance, type 2 diabetes, and other diseases. The postpartum period offers a window of opportunity to modify eating and activity patterns associated with obesity. With the NCI, the OBSSR co-funds research to test Balance Adolescent Lifestyle Activities and Nutrition Choices for Energy (BALANCE), a multilevel intervention designed to reduce overweight in postpartum teens, as measured by change in body mass index (BMI). This work examines whether all or part of improvements in BMI can be explained by changes in adolescent behavior through replacement of "obesogenic" patterns (e.g., soda, high-fat snack intake, excess portion size, and sedentary activity) with "energy" patterns (e.g., low fat milk/water consumption, fruit and vegetable intake, appropriate portion size, and walking), and by improvements in knowledge, modeling, and social support. This study is being conducted in collaboration with Parents as Teachers (PAT), a national parent education organization located in more than 3,108 PAT-affiliated sites across all 50 states in the U.S. This innovative project is the first of its kind to: (1) prevent or reduce the development of long-term overweight among high-risk postpartum teens; (2) test a diet and activity intervention that combines one-to-one personal mentoring at home with group intervention in the classroom setting plus Internet activities supporting both approaches; and (3) secure a foundation for disseminating an empirically tested intervention to 26,000 teen parents located in PAT sites across the nation.

Violence, Distress, and Parenting

Violence exposure among children and adolescents is a well-recognized problem, but it is usually conceptualized as either directly experienced or witnessed maltreatment occurring at the interpersonal or community level. In communities of color, this definition is inadequate because it does not take account of the multiple other sources of exogenous

violence exposure. A study co-funded by the OBSSR and the NIMH examines the processes and mediators by which violence exposure may adversely affect young mothers of color and their children. It also documents the buffering or moderating effects of specific psychological resources. Based on a theoretical model, violence is defined across a continuum including interpersonal, community, and contextual elements (e.g., racism, acculturative stress, and neighborhood deprivation). Effects of interest include measures of maternal psychological distress, parenting, and child behavior. Psychological resources, including ethnic identity and adaptive coping, are evaluated for their role in buffering the effects of violence. This study will describe: (1) the association of violence exposure to maternal distress and parenting; (2) the association of psychological resources to maternal distress and parenting (buffering); and (3) the association of maternal violence exposure and psychological resources to child behavior.

Distress, Social Support, and Ovarian Cancer

Ovarian cancer is the second most common gynecologic cancer. Because of low rates of survival for the majority of ovarian cancer patients, identification of factors contributing to tumor growth and progression is of paramount importance. Although relationships between psychosocial factors and immunity have been extensively documented, there has been little investigation of relationships between psychosocial factors and cytokines involved in angiogenesis, the formation of new blood vessels that enhance tumor growth. These cytokines include interleukin-8 (IL-8), interleukin-12 (IL-12), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF). VEGF, one of the key promoters of tumor angiogenesis, is associated with poorer ovarian cancer survival. VEGF is influenced by a variety of cytokines, hormones including cortisol, and by sympathetic activation. Reports have shown that ovarian cancer patients reporting greater social support had significantly lower serum VEGF at presurgery, whereas those reporting greater feelings of distress had higher VEGF. Additionally, in an in vitro model, stress hormones, such as norepinephrine, have been observed to induce production of VEGF from an ovarian tumor cell line. These effects are further augmented by cortisol. These novel findings, coupled with known hormonal modulation of other angiogenic cytokines, highlight the possibility that psychosocial factors may directly influence angiogenesis and thus tumor progression in ovarian cancer. A five-year prospective longitudinal study, co-funded by the OBSSR and the NCI, will investigate relationships among psychosocial factors and four angiogenic cytokines: VEGF, IL-6, IL-8, and IL-12. The study will include 154 ovarian cancer patients in a clinical setting. These cytokines are selected because of their critical role in ovarian cancer growth and progression. Measurements of cytokines and psychosocial factors will be taken at presurgery and at intervals up to nine months postsurgery; disease progression will be assessed until 18 months postsurgery. The significance of these findings is that they will investigate a novel mechanism by which biobehavioral factors in ovarian cancer patients may contribute to tumor growth and disease progression. Findings will have implications for innovative behavioral and pharmacological intervention strategies for ovarian cancer patients.

OFFICE OF RARE DISEASES

The goals of the Office of Rare Diseases (ORD) are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have one of the approximately 7,000 rare diseases known today. The ORD collaborates with the NIH ICs and Offices to stimulate rare diseases research activities, foster collaboration with other entities, nationally and internationally, and support the following activities:

- An extramural research program that includes a network of rare diseases clinical research centers and the training of rare diseases researchers;
- An intramural research program to stimulate clinical research on rare diseases, including the training of researchers interested in rare diseases and in clinical and biochemical genetics;

- A scientific conferences program that responds to scientific opportunities and stimulates research where research progress may be slow or where little research exists;
- An information center to supply useful information on rare or genetic diseases to the public, researchers, and health care providers;
- Activities to assist national patient advocacy groups in becoming research partners with the NIH by developing a better understanding of the breadth and inclusiveness of NIH research programs;
- The Collaboration, Education and Genetic Test Translation pilot program that translates genetic tests for rare diseases from the research laboratory to the clinic, thereby making the tests available to the public; and
- Development of a Web-based, publicly accessible inventory of repositories of human biospecimens for research on rare and common diseases.

Accomplishments

Rare Diseases Clinical Research Network: Lymphangioleiomyomatosis

Since FY 2003, the ORD has collaborated with several NIH ICs, including the NCRR, NHLBI, NICHD, NIAMS, NIDDK, and NINDS, to support the Rare Diseases Clinical Research Network. The network consists of 10 consortia, each of which focuses on a group of rare diseases. In addition the network includes a data and technology coordinating center that serves all consortia.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is one of the diseases under study in the Rare Lung Diseases Consortium. This disease affects almost exclusively women of childbearing age. LAM is typically slowly progressive. Histopathologic hallmarks of the disease include infiltration of the peribronchiolar, perilymphatic, perivascular, and alveolar interstitium with atypical smooth muscles cells and cystic destruction of the lung parenchyma. There are currently no proven therapies for LAM.

For LAM, one protocol has been approved. The protocol, Multicenter International LAM Efficacy of Sirolimus (MILES) Trial, assesses the safety of Sirolimus administered orally or a placebo to assess the effect of Sirolimus on biological and clinical markers of lung function, including spirometry findings, dyspnea, quality of life, lung volume, diffusion, oxygenation, and exercise tolerance. The consortium expects to enroll 240 patients and 240 controls.

Rett Syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder that predominantly affects females and is characterized by severe cognitive impairment, autistic behavior, stereotypic movements, respiratory irregularities, and frequently seizures. RTT is one of the three syndromes investigated in the Angelman, Rett, and Prader-Willi syndromes Consortium. Ultimately, this consortium will provide RTT patients and their physicians with useful information about the syndrome; link patients with doctors who specialize in the syndrome; help patients learn about and get involved with clinical trials that may help in the treatment of their illness; research new treatments for the syndrome; ensure that clinical trials are held in several locations across the U.S. instead of in a single hospital; better understand, diagnose, and treat the syndrome; and provide better training for doctors and medical students about RTT.

In 2006, the Rett Syndrome Natural History Clinical Protocol was approved, and the consortium has enrolled 479 research participants. The purpose of this protocol is to establish a phenotype-genotype correlation over a broad spectrum of RTT phenotypes including the longitudinal pattern of progression of clinical features, quality of life, and longevity across this cohort. Patients will receive annual evaluations (for those 13 years or older) or biannual evaluations (for those through age 12). For information about a scientific conference on RTT, please see the scientific conference section that follows.

Congenital Adrenal Hyperplasia

The Rare Genetic Steroid Disorders Consortium is an integrated international group of academic medical centers, patient support

organizations, and clinical research resources. The consortium was formed to conduct clinical research in genetic disorders of steroid metabolism, to improve the care of individuals affected with these disorders, to train young investigators in the study and care of these disorders, and to serve as a resource of information about these disorders. The overall objective is to improve the care of patients with rare genetic steroid disorders.

The diseases studied include congenital adrenal hyperplasia that can affect both boys and girls. Congenital adrenal hyperplasia is a family of inherited disorders of the adrenal glands. Congenital adrenal hyperplasia includes a severe form, classical congenital adrenal hyperplasia, with profound 21-hydroxylase deficiency; there is also a mild form, called non-classical congenital adrenal hyperplasia, which has a lesser deficiency of 21-hydroxylase.

Congenital adrenal hyperplasia can represent the classical form that can be virilizing, resulting not only in reduced secretion of cortisol but also in increased secretion of male-like hormones. These male-like hormones masculinize the female fetus in utero so that the genitalia are ambiguous. Congenital adrenal hyperplasia can be diagnosed prenatally, following amniocentesis or chorionic villus sampling (CVS). CVS is a prenatal test that detects chromosomal abnormalities. Classical CAH can be treated prenatally. This can prevent masculinization of the genitalia of affected females.

Two protocols of relevance to women's health are pending approval:

- Modified Genes in 21-Hydroxylase Deficiency: Long-term Outcome in Offspring and Mothers of Dexamethasone-Treated Pregnancies at Risk for Classical Congenital Adrenal Hyperplasia; and
- Hyperplasia Owing to 21-Hydroxylase Deficiency.

Scientific Conferences

The ORD co-funded three scientific conference of importance to women's health:

- **Rett Syndrome**
  Over the years, the ORD has co-funded several scientific conferences on RTT. Most recently, in 2006, the ORD co-funded a conference called Clinical Trials in Rett Syndrome: Potential for Early Intervention. Conference participants assessed the state-of-the-art research in clinical trials and early intervention in RTT and identified those areas where current knowledge is limited. The conference provided a forum for scientists to exchange scientific information regarding RTT diagnosis and treatment; develop recommendations for future research on clinical trials and related issues in RTT; and stimulated the interest and involvement of additional researchers, including trainees and junior faculty from different disciplines in the field of RTT diagnosis and treatment. The proceedings of the conference will be published in the Journal of Child Neurology.
- **Preeclampsia: A Pressing Problem**
  The purpose of this scientific conference was to bring together leaders in the field to discuss their diverse research areas, identify scientific gaps, and stimulate collaborative research. The identification of scientific gaps will be used in planning future research initiatives. There are plans to publish an executive summary of the proceedings in a scientific journal for dissemination to the scientific community.
- **The FMR1 Premutation and Premature Ovarian Failure: Worldwide Community Guideline Development**
  The goals of this conference were to raise awareness among clinicians regarding the association of premature ovarian failure and steroidogenic cell autoimmunity and the potential for developing autoimmune adrenal insufficiency, a potentially fatal condition. The process of bringing together experts in the field was used as a nidus around which to develop multicenter collaborations to advance research in this field.

Genetic and Rare Diseases Information Center

The ORD supports, with the NHGRI, the Genetic and Rare Diseases Information Center (GARD). The GARD provides information to patients and their families, health professionals, researchers, and the public. The information center became more accessible to minority and underserved populations through services in Spanish, in addition to English, and a more user-friendly Web-based approach. Since its inception in September 2001, the information center has responded to approximately 15,000 inquiries about 4,400 rare diseases and an additional 3,000 inquiries about genetic but not rare diseases as well as questions about broader health issues.

A customer service satisfaction survey of the services of the information center showed that:

- Typically, information center customers who responded to the survey were white, non-Hispanic, English-speaking females between the ages of 31 and 40 with a postgraduate education.
- Customers shared or planned to share the information they received from the information center with family members or friends; most of the customers describe themselves as a family member or friend of the individual for whom they were seeking information.

In response to future requests for information, the GARD will modify its approach by making information available on the ORD Web site in addition to its direct services by e-mail, telephone, or letter. Also, efforts will be undertaken to provide services to the broadest possible audience through culturally appropriate outreach activities to increase awareness of the service among minority populations, such as African Americans, Asians, and domestic Hispanics or Latinos. Such outreach efforts would be primarily directed toward women of various subpopulations through a number of community-based institutions including churches, community centers, community health services, and other community-based organizations.

Office of AIDS Research

The Office of AIDS Research (OAR), located within the Office of the Director of the NIH, was established in 1988. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every NIH IC. The NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. This diverse basic, clinical, and behavioral research portfolio demands an unprecedented level of scientific coordination and management of research funds. The OAR coordinates the scientific, budgetary, and policy elements of NIH AIDS research. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, the OAR ensures that research dollars are invested in the highest priority areas of scientific opportunity. As such, the OAR represents the roadmap for NIH AIDS research, allowing NIH to pursue a united research front against the pandemic.

Accomplishments

Trans-NIH Strategic Plan Addresses Research Specific to Women and Girls

The OAR develops the annual comprehensive Trans-NIH Plan for HIV-Related Research. The plans for FY 2005 and 2006 were developed through the annual planning process established by the OAR to identify the most compelling scientific priorities to lead to better therapies and prevention strategies for HIV infection and AIDS. The OAR has established an effective model for developing a consensus on the scientific priorities of the plan. The OAR has established trans-NIH Coordinating Committees to develop the various sections of the plan and then convenes planning groups composed of NIH scientists and experts from academia and industry, as well as representatives from the communities most affected by AIDS. The plan serves as the framework for developing the annual NIH AIDS budget; for determining the use of NIH AIDS-desig-

nated dollars; for tracking and monitoring expenditures; and for informing the scientific community, the public, and the AIDS-affected community about NIH AIDS research priorities. The overarching themes of the plan are: a strong foundation of basic science; research to prevent and reduce HIV transmission, including vaccines, microbicides, and behavioral interventions; research to develop better therapies for those who are already infected; international research, particularly to address the pandemic in developing countries; and biomedical and behavioral research targeting the disproportionate impact of AIDS on minority populations in the U.S.

The plan establishes the NIH AIDS research agenda in the following areas of emphasis: vaccines; therapeutics; etiology and pathogenesis; natural history and epidemiology; behavioral and social science; training, infrastructure, and capacity building; and information dissemination. Research relevant to the needs of women is addressed in all of these areas. The FY 2005 and 2006 plans also include the following cross-cutting research areas: women and girls; microbicides; HIV prevention research; racial and ethnic minorities; and international research. Issues unique to the research needs of women are particularly highlighted in the sections below on microbicides and women and girls.

The trans-NIH Coordinating Committee and outside experts identified the following priorities for research on women and girls in the strategic plans for FY 2005 and 2006.

- Study the biology of the reproductive tract and rectum of HIV-infected and HIV-uninfected women and girls, integrating studies of physiology, immunology, microbiology, and anatomy;
- Elucidate a range of host-virus interactions through the course of HIV infection (in particular, during primary HIV infection) and across the lifecycle in women and girls;
- Develop and continue clinical studies—including biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social—to ascertain the effects of sex and gender in HIV infection among women and girls and to ensure dissemination of resulting information;
- Enhance basic behavioral and social research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences—including gender-based stigma and discrimination—and integrate this work into the design and evaluation of HIV prevention and care interventions;
- Explore factors that influence the development, adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition, and ensure dissemination of resulting information; and
- Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.

In the important area of microbicides research, the trans-NIH Coordinating Committee and outside experts identified the following priorities in the strategic plans for FY 2005 and 2006.

- Foster the development of microbicides consisting of exogenous and endogenous agents and based on specific biological and physiological pathways involving HIV transmission across the epithelia.
- Identify and standardize relevant, practical, and accessible methodologies to assess preclinical and clinical safety and activity of microbicides.
- Foster the development of combination approaches, such as chemical and physical barriers, and of microbicides containing multiple active compounds with different chemical classes, specificities, and mechanism of action in acceptable formulations to prevent transmission and acquisition of HIV and other STIs.
- Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from multiple scientific disciplines.

- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase I/II/III microbicide trials.
- Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, user acceptability, sexual behaviors, and the identification and development of reliable and valid behavioral tools and measurement techniques for use in trials.
- Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.

Microbicide Research Initiative

To further enhance the area of microbicide research, the OAR provided key support for the 2006 International Microbicides Conference, which provided funding to allow scholarships for researchers from developing countries. The OAR announced a major new microbicide research initiative to enhance NIH commitment to microbicide research, to better manage and coordinate the NIH microbicide portfolio, and to elevate the scientific priority and funding for this important area within the prevention research agenda. The OAR is reorganizing its scientific staff to add a new section dedicated to microbicide research and other issues relevant to women. This new OAR section will have responsibility for coordinating, planning, budgeting, and facilitating trans-NIH microbicide research. The OAR has utilized its unique budget authorities to ensure that funding for microbicide research is increasing, even in a time of budgetary constraints. The OAR also revised its AIDS Research Information System to track all trans-NIH investments in and expenditures on microbicide research.

To catalyze efforts to address the priorities established in the strategic plan, the OAR provided funding for the Microbicides Innovation Program, a collaboration of the OAR, the ORWH, the NIAID, the NICHD, and the NIMH. The Microbicides Innovation Program funded 15 grants addressing pressing issues in microbicides development research. Some of these grants included: Identification and Preclinical Testing of Microbicides; Topical Immune-modulatory Strategies to Prevent HIV Transmission; Recombinant CCR5 Inhibitors for Topical Microbicides; Development of N-peptides for Use in HIV Topical Microbicides; An In Vitro Model of Cell-associated HIV-1 Transmission; and Development of Tissue Explant Models for Microbicide Evaluation.

Prevention Science Initiative

At the recommendation of the OAR Advisory Council, the OAR established a Prevention Science Initiative to provide seed funds to jump-start innovative concepts in prevention research. The OAR provided pilot funds to supplement peer-reviewed projects submitted by the NIH ICs. The OAR supported a number of research projects that included components directed toward women. Among these were studies to integrate prenatal care to reduce HIV/STDs, to engage health care providers in female condom promotion, to synchronize HIV prevention strategies with HIV treatment guidelines, and to determine effectiveness of HIV interventions among women in developing countries.

APPENDIX A

Ad Hoc Research Subcommittee of the Coordinating Committee on Research on Women's Health, FY 2005

Representative	*Title*	*Institute, Center or Office*
Elaine Collier, M.D., F.A.C.P. *Chair*	Assistant Director for Clinical Research	NCRR
Frank Bellino, Ph.D.	Program Officer	NIA
Mary Blehar, Ph.D.	Program Officer	NCI
Maria Teresa Canto, D.D.S., M.P.H.	Director, Epidemiology Research Program	NIDCR
Carolyn Deal, Ph.D.	Chief, STD Branch	NIAID
Eleanor F. Hoff, Ph.D.	Health Science Policy Analyst	NIDDK
Karen A Johnson, M.D., Ph.D., M.P.H.	Chief, Breast and Gynecologic Cancer Research Group	NCI
Sooja Kim, Ph.D.	Chief, EMNR IRG	CSR
Cheryl Kitt, Ph.D.	Director, Extramural Program	NIAMS
Anna Levy, M.S.	Deputy Director, Office of NCI Women's Health	NCI
Pamela Marino, Ph.D.	Program Director	NIGMS
Merle Myerson, M.D., Ed.D.	Medical Officer	NHLBI
Mary Frances Picciano, Ph.D.	Senior Nutrition Research Scientist	ODS
Susan Solomon, Ph.D.	Senior Advisor	OBSSR
Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator	NIDA
ORWH Liaisons		
Lisa Begg, Dr.P.H., R.N.	Director of Research Programs	ORWH
Loretta Finnegan, M.D.	Medical Advisor	ORWH
Charisee Lamar, Ph.D., M.P.H.	Program Officer	NIAMS

Ad Hoc Research Subcommittee of the Coordinating Committee on Research on Women's Health, FY 2006

Representative	*Title*	*Institute, Center or Office*
Elaine Collier, M.D., F.A.C.P. *Chair*	Assistant Director for Clinical Research	NCRR
Mary Blehar, Ph.D.	Health Scientist Administrator	NIMH
Maria Teresa Canto, D.D.S., M.P.H.	Director, Health Promotion and Community-Based Research Program	NIDCR
Carolyn Deal, Ph.D.	Chief, STD Branch	NIAID
Eleanor F. Hoff, Ph.D.	Health Science Policy Analyst	NIDDK
Karen A Johnson, M.D., Ph.D., M.P.H.	Chief, Breast and Gynecologic Cancer Research Group	NCI
Sooja Kim, Ph.D.	Chief, EMNR IRG	CSR
Cheryl Kitt, Ph.D.	Director, Extramural Program	NIAMS
Anna Levy, M.S.	Deputy Director, Office of NCI Women's Health	NCI
Pamela Marino, Ph.D.	Program Director	NIGMS
Mary Frances Picciano, Ph.D.	Senior Nutrition Research Scientist	ODS
Catherine Roca, M.D.	Chief, Women's Mental Health Program	NIMH
Susan Solomon, Ph.D.	Senior Advisor	OBSSR
Cora Lee Wetherington, Ph.D.	Women and Gender Research Coordinator	NIDA

ORWH Liaisons

Lisa Begg, Dr.P.H., R.N.	Director of Research Programs	ORWH
Madeline Turkeltaub, R.N., Ph.D., C.R.N.P.	Deputy Director, NIAMS Extramural Program	NIAMS

APPENDIX B
*Office of Research on Women's Health Research Summaries, FY 2005**

Aging

▶ Title: *Phytoestrogens and Aging: Dose, Time and Tissue* NIA
P.I.: William Helferich, Ph.D.
Institution: University of Illinois, Urbana-Champaign
Grant No.: 5 P01 AG024387-02
Keywords: aging, dietary supplements, breast cancer, estrogen, nutrition
Study Type: Basic
Award: $100,000

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 Program 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 preclinical 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: *Health, Illness, and Social Life at Older Ages* NIA
National Social Life Health and Aging Project
P.I.: Linda Waite, Ph.D.
Institution: University of Chicago
Grant No.: 5 R01 AG021487-02
Keywords: sexuality, aging, mental health, prevention, behavioral and social science
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 policy makers 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.

*The abstracts in this appendix are written by the Principal Investigator (PI) and are copied here from the NIH CRISP database, which is available at http://www.nih.gov.

APPENDIX C
Office of Research on Women's Health Research Summaries, FY 2006*

Aging

▶ Title: *Phytoestrogens and Aging: Dose, Time, and Tissue* NIA
P.I.: William Helferich, Ph.D.
Institution: University of Illinois, Urbana-Champaign
Grant No.: 5 P01 AG024387-03
Keywords: aging, dietary supplements, breast cancer, estrogen, nutrition
Study Type: Basic
Award: $97,650

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 Program 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: *Health, Illness, and Social Life at Older Ages* NIA
National Social Life Health and Aging Project
P.I.: Linda Waite, Ph.D.
Institution: University of Chicago
Grant No.: 5 R01 AG021487-03
Keywords: sexuality, aging, mental health, prevention, behavioral and social science
Study Type: Clinical
Award: $244,125

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 policy makers 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.

*The abstracts in this appendix are written by the Principal Investigator (PI) and are copied here from the NIH CRISP database, which is available at http://www.nih.gov.

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 57-84 will be followed longitudinally in two waves over five 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; 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.

▶ Title: *California Native American Research Center for Health (NARCH-Indian Health Service)* NIGMS

P.I.: Deven R. Parlikar, M.B.A.
Mario Garrett, Ph.D.

Institution: Indian Health Council
San Diego State University

Grant No.: 1 S06 GM074084-01

Keywords: Native American, care-giving, elderly

Study Type: Clinical

Award: $25,000

The California Native American Research Center for Health (CA-NARCH) is a partnership of tribal and university organizations committed to working together to reduce health disparities in Native American populations and to increase the number of Native American (NA) scientists and health professionals. The Southern California Tribal community, which ranges from the California-Mexico border to Riverside County with 17 reservations, is the service area of the CA-NARCH project. The Indian Health Council, located in North San Diego County, is the lead agency, and houses the core administrative/research center. The university partners are San Diego State University and the University of California, San Diego. The goals of the CA-NARCH are to (1) develop a cadre of NA scientists and health professionals engaged in biomedical, clinical, behavioral, and health services research who will be competitive in securing NIH and AHRQ funding; (2) increase the capacity of both research institutions and NA organizations to work in partnership to reduce distrust by NA communities toward investigators in research; and (3) encourage competitive research linked to the health priorities of the native organizations and to reduce health disparities. Goal 1 will be accomplished by further implementing student and faculty development programs. The core administrative/research center will continue to focus on Goal 2. The CA-NARCH has begun the process of developing new research Initiatives to address Goal 3. In addition, this application includes two specific research projects and a pilot project proposed by one of our Native American faculty members: 1) examination of the association of Type II diabetes with active and passive tobacco exposure in Southern California Native Americans; (2) examination of perceived burden and resilience among caregivers of frail Native American elders in San Diego County; and (3) examination of alcohol consumption patterns and knowledge of fetal alcohol syndrome among Native American women of childbearing age.

▶ Title: *Caregivers' Strengths-Skills: Managing Older CA Patients* NCI
P.I.: Victoria H. Raveis, Ph.D.
Institution: Columbia University Health Sciences, New York, NY
Grant No.: 1 R01 CA115315-01
Keywords: symptom management, palliative care, behavioral intervention, low income, caregiving, quality of life, depression
Study Type: Clinical
Award: $50,000

We propose to implement and evaluate the efficacy of a short-term problem-solving skills training program for familial caregivers to lower income older (60+) post-treatment cancer patients. The goal of the intervention is to equip family caregivers with problem-solving skills and knowledge that will provide them with a more adaptive means of attending to any symptoms their elderly relative may be experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the post-treatment period, we propose that we will be able to impact patients' health related quality of life, by fostering enhanced symptom recognition, improved symptom control, advocacy with health professionals, and adherence to symptom management options. Familial caregivers to older cancer patients who have completed active treatment will be accrued from Community/Migrant Health Centers (C/MHCs). Caregivers and patients will be followed for ten months. The specific aims are to: (1) Deliver a brief problem-solving training program with regard to symptom management ("Problem-solving") to enhance caregiver skills (i.e., perceived self-efficacy, social problem-solving and communication) of familial caregivers to older post-treatment cancer patients; (2) Evaluate the efficacy of problem-solving in enhancing caregiver skills, relative to participating in a caregiver support group ("Support"): (a) Assess short- and long-term change in caregiver skills reported by caregivers assigned to either the Problem-solving condition or the Support condition; and, (b) Compare change reported by caregivers in the Problem-solving condition, relative to reports by those in the Support condition; (3) Assess the impact of change in caregiver skills on: (a) Change in patients' symptomology and physical functioning, depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with care ("patient outcomes"); (b) Change in caregivers' depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with patient care ("caregiver outcomes"); (4) Disseminate information that informs family training in palliation and symptom control to participating C/MHCs and other C/MHCs serving these populations, contingent on demonstrating beneficial program outcomes.

Alcohol and Other Substance Abuse

▶ Title: *Sex Differences in Opioid Analgesia* NIDA
P.I.: Anne Z. Murphy, Ph.D.
Institution: University of Maryland, Baltimore
Grant No.: 5 R01 DA16272-04
Keywords: opioids, gender, pain, analgesia
Study Type: Clinical
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 animals models of acute pain, the effective dose of morphine is approximately 5-lOx 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 gray (PAG)

and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. Our 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. Our 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. In summary, 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: *Reducing Alcohol and Risks Among Young Females* NIAAA
P.I.: Lydia N. O'Donnell, Ph.D.
Institution: Education Development Center, Newton, MA
Grant No.: 5 R01 AA014515-03
Keywords: alcohol, African American, Latina adolescent females, HIV/ AIDS, alcoholism, basic and social science, infectious diseases, minority health
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% 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 under-addressed 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 (PM) shown to influence adolescent risk behavior will be targeted: parental monitoring (P-PM), household rule setting (HR-PM), and communication (C-PM).

▶ Title: *Substance Use and Girls: Stress, Hormones, and Puberty* NIDA
P.I.: Judy A. Andrews, Ph.D.
Institution: Oregon Research Institute, Eugene
Grant No.: 1 R21 DA018414-01A1
Keywords: hormones, puberty, substance abuse, stress, girls
Study Type: Clinical
Award: $171,563

While girls' use of cigarettes, alcohol and marijuana is less than that of boys in the early elementary years, the prevalence of girls' substance use quickly catches up to and surpasses that of boys by 8th grade. The proposed study is a pilot for a primary study investigating the processes related to the initiation and escalation of substance use among girls in early adolescence focusing on three domains, stressful events, pubertal maturation and timing, and hormonal influences. In the general model guiding

the primary study, these domains are related to early substance use among girls through daily affect, aggression, depression, and affiliation with substance using peers. The specific aims of this study are: (1) To examine the feasibility of an intensive multi-method assessment conducted with 5th and 8th grade girls and their mothers assessing girls' life stress, emotional responses, pubertal maturation and hormones across the menstrual cycle. (2) To examine the variability, reliability and validity of daily and weekly measures of emotional responses, as measured by daily affect ratings, association with substance-using peers, and affiliative coping, for 5th and 8th grade girls and to examine the amount and timing of daily and weekly data required to obtain adequate samples of these variables and hormonal levels. The investigators will also assess the psychometric properties of some of our questionnaire-based measures, with a particular focus on the 5th grade sample. (3) To obtain estimates of effect sizes for: (a) between participant bivariate relations among chronic and episodic stressful events, hormonal levels, and precursors to substance use as a function of grade (5 vs. 8th) and pubertal timing (early vs. on-time/late); and between these variables and early substance use for 8th graders; and (b) within participant bivariate relations between hormonal levels, emotional responses, affiliative coping, and affiliation with substance-using peers, as a function of grade and pubertal timing. To address these aims, the investigators will assess 80 girls, 40 in both the 5th and 8th grade, with 20 early maturers in each grade using multiple methods, including questionnaires completed by both mothers and girls, a Life Stress Interview to assess chronic and episodic stress, and an assessment of the girls' physical maturation by a female nurse. For a minimum of four weeks, they will obtain weekly measures of estradiol, testosterone, progesterone and cortisol, as well as momentary and end of day assessments using an Electronic Personal Data Assistant (PDA). All assessments will be timed to menstruating girls' menstrual cycle, with timing of non-menstruating girls yoked to that of menstruating girls.

▶ Title: *Impulsivity Related to Cocaine Dependence and Trauma* NIDA

P.I.: Angela E. Waldrop, Ph.D.
Institution: Medical College of South Carolina, Charleston
Grant No.: 1 K23 DA018718-01A1
Keywords: post-traumatic stress disorder (PTSD), substance use disorder (SUD), HIV risk behaviors, impulsivity, sexual abuse, minorities, African-American, Hispanic
Study Type: Clinical
Award: $87,440

Training and research plans outlined in this proposal are meant to prepare the candidate to begin an independent research career in which she will design and conduct research on substance use, PTSD, and risky behaviors, with an emphasis on their relationship to impulsivity. The major training goals of the candidate are (a) develop expertise in SUD's: assessment, treatment, and research, (b) develop expertise in comorbidity of SUD's and PTSD, (c) develop expertise in human laboratory research and behavioral measurement of impulsivity, (d) gain expertise in behavioral HIV risk research, (e) enhance skills in grant writing and management, and (f) increase expertise in advanced statistical analyses. The specific aims of the research plan are to (a) investigate impulsivity among women with and without cocaine dependence and with and without at least sub threshold PTSD related to sexual trauma, and (b) to examine the relationships among HIV risk behaviors and the laboratory and self-report measures of impulsivity. The findings of the proposed study will then be used to inform future research in the area of impulsivity among women with co morbid substance use disorders and PTSD, perhaps leading eventually to the development of an intervention to address the harmful consequences of a variety of impulsive behaviors. The candidate has chosen three outstanding co-sponsors and one consultant to assist her in the development of the skills necessary to achieve the training goals and complete the proposed research plan. Dr. Kathleen Brady, the primary mentor, has a substantial record of research on substance use disorders and PTSD. Dr. Heidi Resnick has significant expertise in trauma-related research, particularly in sexual assault populations. Dr. Warren Bickel has published extensively in the area of impulsivity research with substance using populations. All

three mentors are highly regarded for their work in their respective fields of research. Each has an extensive record of federal funding and mentoring junior colleagues. The research environment in Clinical Neuroscience at MUSC is an ideal environment for the candidate to meet her goals with a long history of successful grant funding, participant recruitment, and advanced research training.

▶ Title: *Tobacco Cessation Treatment for Pregnant Alaska Natives* NIDA
P.I.: Christi Patten, Ph.D.
Institution: Mayo Clinic, Rochester, MN
Grant No.: 1 R21 DA019948-01
Keywords: tobacco use, tobacco cessation, treatment development, women, pregnant, culturally-relevant, minorities, Alaska Natives
Study Type: Clinical
Award: $146,700

Tobacco use is the single largest cause of premature and preventable death in the U.S. The prevalence of tobacco use among adults is currently highest among Alaska Natives. Over 50% of Alaska Native women residing in the Yukon-Kuskokwim (Y-K) Delta of western Alaska use smokeless tobacco or smoke cigarettes during pregnancy. Alaska Natives of this region are of Yup'ik or Cup'ik Eskimo, or Athabascan Indian ethnicity. No prior work has evaluated tobacco use interventions for pregnant Alaska Native women. This proposal builds on our successful partnership and track record of collaboration with Y-K Delta Alaska Natives. The objective of this proposal is to develop and pilot test a novel, culturally-tailored behavioral approach to tobacco cessation for pregnant Alaska Native women. As a result of this project, the investigators expect they will have developed a replicable, feasible, and acceptable counseling intervention, the efficacy of which can be tested in future larger-scale randomized clinical trials. Social cognitive (learning) theory is the conceptual basis for the proposed intervention. This project will take place in two phases. In Phase 1, a multi-component, culturally-tailored, tobacco use intervention with and for Alaska Native pregnant women, including a videotape and brief telephone counseling will be developed. This work will include development of a counselor manual and development of the intervention with focus groups. During this phase, 10 pregnant women will complete the protocol, which will be modified and refined based on feedback from participants and counselors. Phase 2, consisting of a pilot clinical trial, will apply a randomized, two group design with assessments at the first prenatal visit (baseline) and at the last prenatal visit approximately 36 weeks gestation. Pregnant women will be recruited and randomized to either a standard (N=30) or enhanced (N=30) tobacco use intervention. The overall health related objective of this line of research is to develop effective treatment programs with and for Alaska Native pregnant women that will ultimately reduce the risk of tobacco-related disease.

▶ Title: *Gender Responsive Treatment for Women in Prison* NIDA
P.I.: Nena Messina, Ph.D.
Institution: University of California, Los Angeles
Grant No.: R21 DA018699-01A1
Keywords: treatment, drug abuse, recidivism, women prisoners, sex/gender, HIV risk behavior, health disparities, minority women, multidisciplinary
Study Type: Clinical, Interdisciplinary
Award: $139,940

This 2-year pilot study will determine the relative effectiveness of a women-focused (WF) treatment program based on relational theory ("Helping Women Recover": Covington, 1999; 2003) compared to a standard prison therapeutic community (TC) treatment program to promote positive behaviors among women inmates. Covington contends that relational theory provides a useful conceptual basis for plan-

ning and implementing appropriate drug abuse treatment services for women offenders, as this model focuses services on women's specific needs and incorporates services that are implemented in a manner that promotes women's psychological growth and helps them to discontinue the cycle of substance abuse and criminal behavior. This curriculum, however, has not been empirically tested. Specifically, 100 women at Valley State Prison for Women in California will be randomly assigned to the WF or TC treatment prison programs. The specific aims of this study are: 1. to pilot test the efficacy of a theoretically based, multi-faceted, WF curriculum to promote positive behaviors among women offenders (i.e., increased self-efficacy and psychological well-being, aftercare participation, and reductions in drug use and recidivism) compared to the impact of a standard prison TC program. 2. To qualitatively assess treatment staff and client perceptions' of the elements of the WF program which are intrinsic to the theoretical basis of the curriculum to refine and improve the WF model of treatment for women in prison. Findings from the proposed pilot study will be used as a platform for the development of a later, larger, and more rigorous study on WF treatment within a prison setting.

Cancer

▶ Title: *Clinical Trials of Two Human Papillomavirus (HPV)-Like Particle Vaccines* NCI

P.I.: Allan Hildesheim, Ph.D.
Douglas R. Lowy, M.D.
Institution: National Cancer Institute, Bethesda, MD
Grant No.: Z01 CP10177
Keywords: human papillomavirus, cervical cancer, vaccine development, STDs
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, 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 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 12,000-15,000 women expected to participate. Eligible women who agree to participate will be administered 3 doses of either a control vaccine or the HPV 16/18 VLP vaccine over a six month period and will be followed for four 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: *Tumorigenic Subversion of Mural Cells in Breast Cancer* NCI
P.I.: Linda Joyce Metheny-Barlow, Ph.D.
Institution: Georgetown University Cancer Center, Washington, DC
Grant No.: R21 CA115829-01
Keywords: breast cancer, tumor-promoting, cell-directed therapies
Study Type: Basic
Award: $129,000

The induction of tumor vasculature, known as the 'angiogenic switch', is a rate-limiting step in tumor progression. Most functional studies have focused on the responses of endothelial cells to pro-angiogenic stimuli; however, there is mounting evidence that the supporting mural cells (smooth muscle cells and pericytes) play a key regulatory role in maintaining a mature, quiescent vasculature. In tumors, mural cell association with the endothelium is decreased and abnormal. Previous work has shown that restoration of functional inhibitory maturation to vasculature by Angiopoietin-1 inhibits tumor growth, suggesting that stabilization of tumor vessels may be a desirable therapeutic goal in the treatment of cancer. The hypothesis underlying this work is that breast cancer cells functionally alter mural cell and endothelial cell contacts and subvert the mural cell from its normal anti-angiogenic role to a vessel-promoting role as part of the angiogenic switch. Paracrine interactions between endothelial cells, mural cells, and breast cancer cells will be studied using in vitro membrane and spheriod models that mimic the organization of the blood vessel wall, as well xenograft models with modified mural cells, in order to address three specific aims. Aim 1 will identify critical alterations in mural cell function in response to breast cancer cells that may contribute to the maturation defect exhibited by the tumor vasculature. Aim 2 will investigate the ability of tumor cells to activate matrix metalloproteases specifically in mural cells as part of the acquisition of a pro-angiogenic functional state. Aim 3 will address whether the differentiation utilization of specific sphingosine-1-phosphate receptors plays a role in the tumor-induced maturation defect and activation of mural cells. Together, these studies will I) provide proof-of-principle that tumors can subvert the function of normally inhibitory mural cells to a tumor-promoting state, and ii) identify pivotal molecular players involved in these activities to serve as targets for future mural cell-directed therapies to restore quiescence to the vasculature.

▶ Title: *Pharmacogenetics of the Endocrine Treatment of Breast Cancer* NIGMS
P.I.: David A. Flockhart, M.D., Ph.D.
Institution: Indiana University-Purdue University at Indianapolis
Grant No.: 2 U01 GM061373-06
Keywords: pharmacogenetics, breast cancer, translational research, tamoxifen (TAM)
Study Type: Basic, Translational
Award: $250,000

Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer, and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but which drug is best for each woman remains unclear. Our work in the first cycle of the Pharmacogenetics Research Network identified, through a series of laboratory and clinical studies, new genetic patterns that predict effects of the estrogen receptor modulator tamoxifen. We now propose to build on these data to examine the influence of an extended series of candidate genes on the effects of the aromatase inhibitor class of drugs and to refine the genetic signatures that predict tamoxifen effects. Our work will involve the following broad specific aims: 1) To identify common genetic variants of the human estrogen receptors and important nuclear coactivators and repressers of these receptors using a combined bioinformatic and direct sequencing approach; 2) To test the hypothesis that these variants alter gene expression or function using in vitro assays; 3) To test the contribution of variants identified during specific aim 1 and 2 to tamoxifen response in the clinical trial of tamoxifen

pharmacogenetics already conducted. 4) To characterize the involvement of genetically polymorphic drug metabolizing enzymes in the human metabolism of the available aromatase inhibitors: letrozole, exemestane and anastrozole in vitro. 5) To test the hypothesis that variants in candidate genes identified in aims 1-4 are associated with well curated phenotypic outcomes, including estrogen metabolite concentrations, pharmacokinetics, hot flashes, breast density, bone metabolism and serum lipid sub fractions in breast cancer patients receiving anastrozole, exemestane and letrozole. The results of this proposal will generate new information that, linked with our novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools key to optimizing drug selection for women with breast cancer and to our understanding of the mechanisms of estrogen action.

▶ Title: *Patient-Centered Communication During Chemotherapy* NCI

P.I.: Douglas M. Post, Ph.D.
Institution: Ohio State University
Grant No.: 1 R21 CA115388-01
Keywords: symptom management, palliative care, pain, depression, fatigue, breast cancer, behavioral intervention
Study Type: Clinical
Award: $50,000

Pain, depression, and fatigue are among the most common disease and treatment-related symptoms experienced by cancer patients. Studies have indicated that communication problems between cancer patients and clinicians are a major barrier to the effective management of these symptoms. This project is designed to address this important problem through the development and evaluation of a PDA-based patient communication intervention for breast cancer patients undergoing chemotherapy treatment. The intervention will be comprised of two integrated components: symptom monitoring and tailored patient communication training. Patients will be asked to complete fatigue, depression, and pain inventories on a PDA at the beginning of chemotherapy and once per week through the completion of treatment. On the day prior to an appointment for chemotherapy treatment, a summary of fatigue, depression, and pain scores will be integrated with a tailored patient communication skills training program and displayed on the PDA for patient viewing. Patients will be taught, through role modeling, how to effectively communicate the types of symptoms they have experienced between treatments. They will also be encouraged to bring the PDA with their symptom summaries to each chemotherapy visit and to share this information with their health care provider. Year one of the project will primarily be devoted to the development and usability testing of the intervention. A feasibility trial will be conducted during the second year. Fifty patients with breast cancer will be recruited into the trial at the start of their chemotherapy treatment. A repeated measures design will be used to assess the effects of the intervention on symptoms of fatigue, depression, and pain over the course of treatment. At the end of treatment, focus groups will be conducted with study participants to assess their responses to the intervention and their perceptions of the system's value to both themselves and future cancer patients. In addition, the feasibility of the project, defined as the proportion of patients recruited into the study and the proportion of patient adherence to instructed use of the system, will be analyzed. Specific aims of the project include: 1) Develop the patient-centered communication intervention; 2) Conduct usability testing to ensure the successful completion of the intervention; 3) Examine study feasibility and patient reactions to the intervention; and 4) Evaluate intervention effects on pain, depression, and fatigue symptoms over time.

Cardiovascular Disease

▶ Title: *Genetics of Early-Onset Stroke* NINDS
P.I.: Steven J. Kittner, M.D.
Institution: University of Maryland, School of Medicine, Baltimore
Grant No.: 5 R01 NS045012-03
Keywords: ischemic stroke, thrombomodulin, protein C, fibrinolysis systems, endothelial protein C receptor, plasminogen activator inhibitor-1, endothelial protein C receptor polymorphisms, African-American, Caucasian, brain disorders, cardiovascular, genetics, prevention
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: *Sex Differences in Purkinje Cell Sensitivity to Ischemia* NINDS
P.I.: Paco Herson, Ph.D.
Institution: Oregon Health Sciences University, Portland
Grant No.: 1 R21 NS052591-01A1
Keywords: stroke, neuroprotection, progesterone, ischemia, neurons, sex hormones
Study Type: Basic
Award: $200,000

Stroke or Brain Attack is a sexually dimorphic disease. Women enjoy protection from stroke relative to men, in part due to endogenous levels of sex steroids, the estrogens and progesterone. While estrogen has been well studied, little is known about progesterone's neuroprotective properties. The steroid is an important but controversial component of hormone therapy in women. Progesterone reduces ischemic brain injury in vivo, however the mechanism is not known. The investigators hypothesize that one important mechanism of neuroprotection is via progesterone's enhancement of GABA-A receptor activity,

counteracting the high levels of excitatory input to neurons during and immediately following ischemia. This R21 application tests this overarching hypothesis, using whole cell voltage-clamp experiments and single cell PCR in cerebellar Purkinje cell (PC) culture, as a novel and initial step in understanding progesterone's neurophysiological actions in complex animal ischemia models. They focus on PCs because of important early observations that PCs, like the well-studied hippocampal CA1 neuron, are uniquely hyper-vulnerable to ischemia. While data from these GABA sensitive cells and cerebral ischemia are few, our recent studies emphasize that non-ischemic female PCs are selectively sensitive to enhancement of GABA-A receptor activity by progesterone metabolites. Furthermore, their preliminary data indicate that female mice require continued exposure of sex steroids to maintain enhanced sensitivity to progesterone metabolites relative to male mice. Therefore, they will test three specific hypotheses 1) Acute progesterone protects PCs from ischemia through activation of the GABA-A receptor. 2) Chronic progesterone enhances female cells to acute progesterone neuroprotection and 3) that chronic progesterone decreases the expression of the gamma-subumt of the GABA-A receptor resulting in increased sensitivity to acute progesterone. Their findings will begin to elucidate the cellular mechanisms of progesterone neuroprotection and sex differences in Purkinje cell response to ischemia.

▶ Title: *Altered Glucose and Lipid Metabolism in Obesity and CVD* NHLBI

P.I.: Maureen J. Charron, Ph.D.
Institution: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 5 R01 HL073163-03
Keywords: metabolic disturbances, cardiovascular disease, insulin-stimulated GLUT4 transporter, diabetes, genetics, obesity, prevention
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 over-express 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.

▶ Title: *Inflammation and Insulin Resistance in Peripheral Arterial Disease* NHLBI
P.I.: Mark A. Creager, M.D.
Institution: Brigham and Women's Hospital, Boston
Grant No.: 3 R01 HL075771-03
Keywords: PAD, CVD, sex differences, inflammatory
Study Type: Epidemiologic (case-control)
Award: $10,000

Patients with peripheral arterial disease (PAD) frequently have functional limitations and symptoms of claudication that impact adversely on their quality of life. Many progress to critical limb ischemia requiring revascularization. Vascular inflammation and insulin resistance are two important and interdependent conditions that are associated with atherosclerosis. Moreover, both inflammation and insulin resistance cause abnormalities in vascular function and insulin resistance interferes with skeletal muscle metabolism. As such, inflammation and insulin resistance provide attractive targets for therapy that could potentially ameliorate the development of symptomatic PAD or improve the function and clinical outcomes of patients with PAD. Accordingly, the applicants propose three specific aims to determine whether inflammation and insulin resistance contribute to the functional and clinical consequences of PAD. First, a prospective, nested, case-control evaluation will be performed to test the hypothesis that baseline plasma levels of inflammatory cytokines (e.g. interleukin (IL)-4, IL-6, IL-18, macrophage inhibiting cytokine-1, CD 40 ligand) among healthy men are associated with the development of future symptomatic PAD. Second, to test the hypothesis that inflammation and insulin resistance contribute to reduced walking distance in patients with intermittent claudication by impairing vascular reactivity and skeletal muscle metabolic function, plasma markers of inflammation and insulin resistance, endothelium-dependent and independent vasodilation (by vascular ultrasonography) and skeletal muscle glucose utilization (by [18F] FDG positron emission tomography) will be measured before and after 12 weeks of treatment with rosiglitazone, atorvastatin or placebo in a 2x2 factorial design protocol. Third, to test the hypothesis that inflammation and insulin resistance are associated with the incidence and progression of vein graft disease in patients undergoing lower extremity vein bypass, functional and morphologic changes in vein grafts (measured by ultrasound and magnetic resonance imaging) will be assessed and related to inflammation and insulin resistance and to a composite clinical outcome of graft occlusion, reintervention or major amputation. It is anticipated that the findings from this investigation will uncover novel pathophysiologic mechanisms and foster a new paradigm for the treatment of PAD.

▶ Title: *Phytoestrogens and Progression of Atherosclerosis* NCCAM
P.I.: Howard Hodis, M.D.
Institution: University of Southern California
Grant No.: 3 U01 AT001653-02S4A1
Keywords: prevention, randomized clinical trial, bone health
Study Type: Clinical
Award: $36,544

This application is a supplement to a recently funded randomized controlled trial, Phytoestrogens in Progression of Atherosclerosis (U01-AT001653). This supplement is focused on the effect of isoflavone-rich soy protein (ISP) supplementation on bone mineral density, bone metabolism and bone turnover in postmenopausal women. Fear and discontent with traditional hormone therapy has resulted in an escalating use of soy products as a postmenopausal therapeutic alternative. However, current information derived from clinical trials of the efficacy of soy on bone health has been limited since studies have been of short duration (mostly 3-12 months) and conducted in small sample sizes. Data concerning the effects of soy on bone health from long-term trials conducted in a large cohort of postmenopausal women are missing. As such, the design, duration and size of the parent trial make it an ideal platform upon which

to adequately assess the effects of ISP supplementation on bone health. Since the central portion of the clinical trial has been funded, a very robust database will be obtained at considerable savings. The objective of this supplement is to investigate the effect of ISP supplementation on bone mineral density, metabolism and turnover in 300 healthy postmenopausal women in a 2.5 year, randomized, double-blind, placebo-controlled trial. The 4 Specific Aims are: 1) To determine the effect of ISP supplementation on bone mineral density; 2) To assess the effect of ISP on markers of osteoblast activity by measuring serum bone-specific alkaline phosphatase; 3) To assess the effect of ISP on markers of osteoclast activity by measuring urinary excretion of N-telopeptide; and, 4) To assess the effect of ISP supplementation on regulation of bone turnover by measuring serum RANKL and osteoprotegerin. We hypothesize that ISP supplementation will attenuate bone loss associated with aging and/or postmenopausal estrogen loss. Providing direct evidence for the efficacy of ISP in reducing osteoporosis with a clinical trial using well-validated measurements of bone mineral density, bone metabolism and bone turnover has immense public health implications for women's health.

Craniofacial

▶ Title: *Brief Focused Treatment for TMD: Mechanisms of Action* NIDCR

P.I.: Mark D. Litt, Ph.D.
Institution: University of Connecticut, School of Medicine, Farmington
Grant No.: 5 R01 DE014607-03
Keywords: temporomandibular disorders (TMD), pain, coping, mood, cortisol, cytokines, behavioral and social science, dental/oral disease, chronic pain conditions
Study Type: Clinical
Award: $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 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 6 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 hand-held 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 follow-up points thereafter up to a 12-month follow-up. 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 TMJD Vulnerability Types* NIDCR
P.I.: Christian S. Stohler, D.M.D.
Institution: University of Maryland Professional School, Baltimore
Grant No.: 5 R01 DE015396-03
Keywords: temporomandibular, pathogenesis, candidate gene, estrogen, dental/oral disease, genetics, chronic pain conditions
Study Type: Basic and Clinical
Award: $100,000

Temporomandibular joint disorders 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 TMJ and Fibromyalgia* NIDCR
P.I.: Dean A. Dessem, Ph.D.
Institution: University of Maryland Dental School, Baltimore
Grant No.: 5 R01 DE015386-03
Keywords: temporomandibular, fibromyalgia, neurons, musculoskeletal, gender, dental/oral disease, chronic pain conditions
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, 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, 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 a) spontaneous and evoked

activity and b) 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 TMJ* NIDCR
P.I.: Phillip R. Kramer, Ph.D.
Institution: Texas A and M University Health Science Center, Dallas
Grant No.: 5 R01 DE015372-03
Keywords: gene, macrophage, rheumatoid factor, dental/oral disease, estrogen, TMJ disorders
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 post-partum 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-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-alpha and IL-1 alpha will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim two 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-alpha and IL-1 alpha promoter sequences. Aim three will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ER alpha and/or ER beta will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

▶ Title: *Mast Cell Role in Masseter Muscle Repair* NIDCR
P.I.: Joyce A. Morris-Wiman, Ph.D.
Institution: University of Florida, Gainesville
Grant No.: 5 R21 DE016317-02
Keywords: TMJ, pain, inflammation, dental/oral disease
Study Type: Basic
Award: $100,000

Temporomandibular disorders (TMD) affect approximately 12% of the US population, predominately women in their childbearing years and of those affected by TMD, greater than 60% 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: *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
Grant No.: N01 DE22635
Keywords: TMJ, medical devices, chronic pain conditions, dental/oral disease
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.

Diabetes

▶ Title: *Diabetes Prevention Program Outcomes Study (DPPOS)* NIDDK
P.I.: Sarah Fowler, Ph.D.
Institution: George Washington University, Washington, DC
Grant No.: 5 U01 DK048489-12
Keywords: diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention, cardiovascular disease
Study Type: Clinical
Award: $300,000

The Diabetes Prevention Program (DPP) addressed its primary objective, establishing the efficacy of lifestyle modification and metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for an average of 2.8 years; however, many important issues remain unanswered. Specifically, whether the decrease in the development of diabetes can be sustained is unknown. Moreover, determining whether the delay or prevention of diabetes will translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease, all of which require more years to develop than the DPP period of study, is critical to establish the true impact of the DPP on public health. The

long-term follow-up study of the DPP, entitled the Diabetes Prevention Program Outcomes Study or DPPOS, is designed to evaluate the long-term effects of active DPP interventions on the development of a) diabetes during a further 5-11 years of follow-up and b) composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both the continued lifestyle intervention and metformin will provide continued separation in the rates of diabetes development, compared with the former placebo group, and that the prevention or delay of diabetes during the DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status. The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

▶ Title: *Gestational Diabetes and Preeclampsia Cytokine Profiles* NIDDK

P.I.: Ravi Thadhani, M.D.
Institution: Massachusetts General Hospital, Boston
Grant No.: 1 R01 DK67397-01A1
Keywords: gestational diabetes, preeclampsia, cytokine, proteomics
Study Type: Clinical
Award: $100,000

Gestational diabetes mellitus (GDM) and preeclampsia (PE) are associated with significant morbidity and mortality during pregnancy and risk for diabetes and cardiovascular disease after pregnancy. Biological mechanisms suggest alterations in specific cytokines (cytokines and growth factors) linked to inflammation, insulin resistance, and angiogenesis lead to GDM and PE. These cytokines may also serve as early markers or disease during pregnancy, and if present postpartum, critical markers for future disease. Currently, no single biochemical measure reliably identifies women at risk for these complex disorders during pregnancy, and those at risk for future disease. Likely, alterations in a specific combination of cytokines ('cytokine signatures') characterize GDM and PE. Limitations in technology and lack of prospective studies have prevented efficient and accurate quantification of cytokine combinations. Careful application of novel, multiplexed profiling techniques to quantify biologically important cytokines in women followed prospectively during pregnancy overcomes these limitations. The investigators will test 3 hypotheses (in serum and urine): 1) Cytokine (TNF-alpha, IL-1beta, IL-6, MCP-1, IL-8) alterations identified early in pregnancy distinguish women who develop GDM or PE, and after pregnancy, characterize these same women; 2) Angiogenesis-related placental growth factors (PIGF, FGF-2) and an inhibitor (sFlt-1) are altered early in pregnancy among women who develop GDM and PE; 3) Disease-specific microarrays quantifying a set of pre-specified highly informative (aims 1, 2) cytokines can be developed, and this prospectively identifies incident GDM and PE. Their ongoing prospective pregnancy cohort permits excellent power and efficiency to test each aim. A multidisciplinary team with expertise in the epidemiology of diabetes and hypertension in pregnancy, placental biology, microarray technology, and bioinformatics will perform an innovative and cost-efficient study to understand the biology of GDM and PE, identify early markers for the conditions and suggest potential for interventions.

Endocrinology

▶ Title: *Estradiol and Hippocampal Development* NINDS
P.I.: Margaret M. McCarthy, Ph.D.
Institution: University of Maryland, Baltimore
Grant No.: 1 R01 NS50525-01A1
Keywords: hippocampus, brain, learning, memory, hypothalamic-pituitary-adrenal (HPA) stress axis, sex differences, cognitive functioning
Study Type: Basic
Award: $333,155

The hippocampus is a brain region regulating two divergent but related life functions; learning and memory and regulation of the hypothalamic-pituitary-adrenal stress axis. The rodent provides a powerful model for investigating the importance of the hippocampus in both these responses. In the adult, the hippocampus is a sensitive target organ for both gonadal and adrenal steroids. Estradiol modulates synaptic plasticity in the CA1 region and improves cognitive functioning on spatial learning tasks. The effects of estradiol on hippocampal development have been less intensively studied and largely framed in the context of sexual differentiation of the brain. In this scenario, neonatal androgens of testicular origin are locally aromatized to estradiol by neurons and thereby exert a masculinizing effect on the neuroarchitechture. However, the investigators recently discovered that contrary to expectation, the developing female hippocampus possesses high levels of estradiol. This lead them to speculate that the developing female hippocampus synthesizes estradiol de novo from cholesterol and this results in levels similar to that of males produced from testicular androgens, thereby reducing sex differences in cognitive functioning in adults. This tenet can be deconstructed into three testable hypotheses: 1) The developing female hippocampus makes estradiol de novo from cholesterol. 2) The developing male hippocampus does not make estradiol de novo from cholesterol but instead derives estradiol from testicular androgen. 3) Developmental estradiol synthesis in females reduces sex differences in cognitive function. The investigators will test each of these hypotheses via three specific aims that involve characterizing the source of estradiol, determining the functional significance of estradiol action to hippocampal development and identification of cellular endpoints modulated by estradiol. These results will be informative to normal hippocampal development and may serve as an entry point into understanding adult sex differences in learning and memory and stress responding.

Gastroenterology

▶ Title: *Improving IBS Outcomes* NINR
P.I.: Margaret M. Heitkemper, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 5 R01 NR04142-08
Keywords: irritable bowel syndrome (IBS), polymorphisms, gender, serotonin, behavioral and social science, digestive disease, chronic pain conditions
Study Type: Translational
Award: $100,000

In the United States, it is estimated that 10-20% 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.: 5 U01 DK 070234-02
Keywords: urinary frequency, bladder pain, patient screening, survey research, quality of life, endometriosis, interstitial cystitis, chronic pain conditions, urologic disease
Study Type: Epidemiological
Award: $200,000

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; (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: *A New Tool to Diagnose Female Urinary Incontinence* NICHD
P.I.: Catherine Bradley, M.D., M.S.C.E.
Institution: University of Iowa Hospitals, Iowa City
Grant No.: 1 K23 HD047654-01A1
Keywords: career development and training, patient-oriented research, clinical trials, urologic disorders, urinary incontinence
Study Type: Basic
Award: $100,000

Catherine Bradley, M.D., M.S.C.E. is a full-time faculty member in the Department of Obstetrics and Gynecology at the University of Iowa. Her long-term goal is to become a successful, independent investigator focusing on patient-oriented research in female urinary incontinence (UI). She has recently completed a Master's program in Clinical Epidemiology, and she intends to pursue further formal research training, specifically in areas of questionnaire development, psychometric analyses and the use of survey data in epidemiologic studies. This award would allow her to pursue a research career development plan that includes additional advanced courses and instruction in biostatistical and epidemiologic methodology, the closely mentored completion of this research protocol, and participation in a broad range of research activities by interacting with established research groups and their ongoing projects. Dr. Bradley's immediate goals for the award period include: 1) complete coursework targeted in areas of research methodology and analysis important to this protocol, 2) further develop her critical thinking skills in clinical and epidemiologic study design and statistical analyses through the mentorship described in this application and by attending seminars and meetings, 3) become involved in multiple types of clinical and epidemiologic research, such as clinical trials and cohort studies, by working closely with her mentors at the University of Iowa and elsewhere, 4) conduct, analyze and interpret results from the proposed questionnaire development research project, 5) present research findings to the scientific community via presentations and publications and 6) develop an area of research expertise that will lead to future study opportunities. As her main research effort, Dr. Bradley proposes to develop and test a Questionnaire for female Urinary Incontinence Diagnosis (QUID). Her hypothesis is that a self-administered symptom-based questionnaire can accurately predict if a woman has stress and/or urge UI. The specific aims are to measure the validity, reliability and responsiveness of the QUID. To fulfill these aims, she will complete a prospective, split-sample longitudinal study of outpatients with UI symptoms. Criterion validity of the QUID will be tested by comparing the QUID'S diagnoses to formalized clinical diagnoses as the gold standard. Precise measurements of the QUID'S sensitivity and specificity in the diagnosis of stress and urge UI will be performed. Reliability, reproducibility and responsiveness of the QUID will be measured. This study will produce a rigorously developed and tested questionnaire, which will be a useful diagnostic tool for clinicians and researchers who wish to accurately predict the underlying diagnoses behind female UI symptoms. The combination of clinical and research resources available at the University of Iowa provides an ideal environment for Dr. Bradley's research career development. Dr. Bradley has the enthusiastic support of the Colleges of Medicine and Public Health, the Department of Obstetrics and Gynecology and her mentors and collaborators.

▶ Title: *Mechanisms of Female Urinary Incontinence in Diabetes* NIDDK

P.I.: Margot S. Damaser, Ph.D.
Institution: Loyola University, Chicago
Grant No.: 1 R21 DK070905-01
Keywords: diabetes, pregnancy, incontinence, vaginal delivery
Study Type: Basic
Award: $187,555

Diabetes mellitus (DM) causes debilitating and devastating complications, including these of the lower urinary tract (LUT), such as urinary incontinence. Women with DM have a higher prevalence of LUT complications, contributing to the high prevalence of urinary incontinence (30-60%) among adult women in the US. In addition, women are at increased risk of later development of stress urinary incontinence due to pelvic floor injuries sustained during vaginal delivery of children. Vaginal delivery causes ischemic injury to tissues of the pelvic floor, including muscle, fascia, and nerves. The pudendal nerve, which innervates the external urethral sphincter and contributes to urinary continence, is particularly vulnerable to ischemia, crush, and stretch during delivery. Type I DM affects women at or before their childbearing years and increases their risk of incontinence after vaginal delivery. However, the mechanistic relationship between DM and urinary incontinence is poorly understood. In pursuit of their common interests, the Principal Investigator, Dr. Damaser, and the co-Investigator, Dr. Daneshgari, have jointly developed a theory that the accumulation of advanced glycosylation end products (AGEs) from prolonged hyperglycemia induces intracellular oxidative stress, limiting the ability of LUT muscles and associated nerves to recover from the injuries sustained during vaginal delivery, particularly pudendal nerve injury. This could provide the mechanism for the relationship between DM and urinary incontinence. This research grant proposes to develop a unique animal model and obtain feasibility and preliminary data for a future R01 application. It proposes development of an animal model addressing both bladder complications of diabetes and gender differences in development of incontinence, a LUT disorder. In addition, it would promote productive research collaboration for the study of the LUT between a clinician (Dr. Daneshgari) and a basic scientist (Dr. Damaser). The Hypothesis of this project is that the response of diabetics to pudendal nerve injury involves 1) a decreased neuroregenerative response and 2) increased duration and severity of incontinence symptoms, both of which are temporally associated with an accumulation of advanced glycated endproducts. Investigators will test this hypothesis with 2 specific aims: (I) Determine if pudendal nerve crush in diabetic animals results in: a. decreased pudendal nerve regeneration and b. increased duration and severity of urinary incontinence symptoms; and (II) Determine if these altered responses in diabetic animals are temporally associated with increased accumulation of AGEs. Techniques to be utilized include cystometry, leak point pressure testing, morphometry, light and electron microscopy, and in situ hybridization of β_{II} tubulin mRNA, mass spectrometry, immunohistochemistry and ELISA. The data from this R21 exploratory research grant will be used to propose a R01 research grant to explore the mechanism of the observed effects. The long-term goals for this project include using this novel animal model to study the mechanism of urinary incontinence in women with DM, to develop & test novel mechanism-based pharmacologic agents, and to develop & test techniques and strategies which could be used to prevent and/or treat incontinence in women with DM.

HIV/AIDS

▶ Title: *Impact of Delivery Models in HIV Health Care* FIC
P.I.: Ximena L. Burbano, M.D.
Institution: Fundacion Santa Fe de Bogota, Bogota, Columbia
Grant No.: 5 R01 TW006218-03
Keywords: HIV/AIDS, health services research, prevention, infectious diseases
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 HIV1 Incidence after Delivery* FIC
P.I.: James N. Kiarie, M.D.
Institution: University of Nairobi, Kenya
Grant No.: 5 R01 TW006640-03
Keywords: HIV/AIDS, postpartum, counseling, prevention, topical microbicides
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-1transmission, 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 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; 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 (AITRP)* FIC
P.I.: Arthur L. Reingold, M.D.
Institution: University of California, School of Public Health, Berkeley
Grant No.: 3 D43 TW000003-06
Keywords: training, virology, HIV/AIDS, infectious diseases
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 International AIDS Training 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 on-going 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 proposal 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; 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, New York, NY
Grant No.: 3 D43 TW000018-18
Keywords: infectious diseases, epidemiology, biosocial, HIV/AIDS, treatment and prevention, rural health
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 preven-

tion 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., PhD, 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% 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 (AITRP)* FIC
P.I.: King K. Holmes, M.D., Ph.D.
Institution: University of Washington, College of Medicine, Seattle
Grant No.: 5 D43 TW000007-18
Keywords: HIV/AIDS, international, prevention, treatment, immunology, infectious diseases, vaccine development
Study Type: Clinical
Award: $50,000

This program proposes to develop a fifth International AIDS Research and Training Program (IARTP) 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) IARTP 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 IARTP 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: a) Strengthening of the infrastructure for field research through training and capacity building in the area, b) Development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, c) 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-term 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: a) Seroprevalence and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, b) Clinical profile of HIV-1 clade C infection in India, c) Cellular immunity to HIV-1clade C viruses and diversity consideration in vaccine development, and d) 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: *Brown/Tufts AIDS International Training & Research Program (AITRP)* FIC
P.I.: Kenneth H. Mayer, M.D.
Institution: Miriam Hospital, Brown University, Providence, RI
Grant No.: 2 D43 TW000237-12
Keywords: HIV/AIDS, training, international, Asian, Pacific Islanders, prevention, women's health, nutrition, metabolic, molecular virology
Study Type: Clinical
Award: $100,000

The Brown/Tufts University Fogarty AIDS International Research Training Program is applying for continued support of its educational activities for the next 5 years, 2005-2009. The AIRTP has trained 48 clinical, laboratory, behavioral, and public health researchers from India, the Philippines, Cambodia, Indonesia, Bangladesh, and Thailand in the previous 5 years in multiple aspects of AIDS research. Trainees have been extremely productive, with almost 70 peer-reviewed publications, more than 100 presentations at all major international AIDS research conferences, participation in many international advisory capacities and organizations, ranging from the WHO to the Gates Foundation. Several trainees have been successful in developing their own independent research programs with R-O1 funding, as well as participation in HPTN, ACTG, and TREAT ASIA networks. In this new cycle the Brown/Tufts ARTP proposes to focus on longer term training, budgeting to provide tuition for at least 5 long-term trainees per year at either Brown or Tufts. Trainees may elect to participate in MPH, Masters Programs in Epidemiology, Biostatistics, or Clinical Decision Analysis, as well as PhD programs. In addition, they have developed 6-month intensive training courses in a variety of clinical research disciplines, including Molecular Virology, Clinical Trial Research Design, HIV Prevention Research, Women's Health, Nutrition and Metabolic Studies, as well as Pharmacology. In order to identify the highest calibre trainees, the AIRTP has developed a formal advisory process, which includes the Directors of several national AIDS programs, Public Health Research Institutes, and Research Universities each of the affiliated countries. In addition, a formal mentoring program has been developed which will ensure that each international trainee is in frequent contact with a designated Brown or Tufts faculty mentor whose research interests are congruent with those of the relevant trainee. Prospective candidates will be proposed by international advisors and their selection with be conducted during the monthly meetings of the Brown-Tufts Fogarty AIRTP Executive Committee, which includes accomplished faculty from all affiliated institutions with diverse academic training and a commitment to international public health training. The Committee will continue to meet monthly to evaluate the progress of each trainee, to consider applications for new trainees into our program.

Immunity/Autoimmunity

▶ Title: *Mechanism Regulating Neutrophil Activation in Pregnancy* NIAID
P.I.: Howard R. Petty, Ph.D.
Institution: Wayne State University, Detroit, MI
Keywords: Autoimmunity, rheumatoid arthritis, pregnancy
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, New York, NY
Grant No.: 5 R01 AI51767-04
Keywords: autoimmunity, hormones, animal models, estrogen
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 3 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: *Predictors of Pregnancy Outcome in SLE and APS* NIAMS

P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 5 R01 AR049772-03
Keywords: thrombosis, pregnancy loss, systemic lupus erythematosus, antiphospholipid antibodies, genetic polymorphisms, recurrent fetal loss, poor fetal outcome, placentas, autoimmune diseases, genetics, prevention
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 6 major clinical centers, and grouped and analyzed according to the presence or absence of aPL and preexisting 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: Johns Hopkins University, Baltimore, MD
Grant No.: 5 R01 AR49125-04
Keywords: systemic lupus erythematosus, cognitive dysfunction, basic behavioral, behavioral and social science, brain disorders, depression, fibromyalgia, mental health
Study Type: Clinical
Award: $100,000

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 10 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: *Antibodies to NR2 in SLE* NIAMS
P.I.: Betty Diamond, M.D.
Institution: Yeshiva University, New York, NY
Grant No.: 5 R01 AR49126-04
Keywords: NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, human tissue, brain disorders
Study Type: Clinical
Award: $80,000

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 tudied 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: *Virginia Mason/UCHSC Autoimmune Center* NIAID

P.I.: George S. Eisenbarth, M.D.
Institution: University of Colorado, Denver
Grant No.: 5 U19 AI50864-05
Keywords: autoimmunity, diabetes, rheumatoid arthritis, genetics, prevention
Study Type: Translational
Award: $200,000

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

▶ Title: *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 AI51973-05
Keywords: autoimmunity, diabetes, autoimmune disease, CD antigen, CD40 molecule, antibody inhibitor, antigen antibody reaction, autoimmune disorder, cooperative study, disease /disorder prevention /control, immunotherapy
Study Type: Basic
Award: $100,000

All three projects of the consortium application are targeted at better understanding induction of long-term tolerance by co stimulation blockade of CD40/CD40L interactions with aCD40L 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 down-modulate 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 AR48045-05
Keywords: scleroderma, immune response, autoimmunity, autoimmune disease, Raynaud's disease, autoantibody, scleroderma, ribonucleoprotein, immunodiffusion, western blotting
Study Type: Translational
Award: $200,000

Systemic sclerosis (scleroderma) is a disfiguring, multi-system 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-1) autoantibodies are quite specific for scleroderma, and are present in precipitating levels in 20-40% 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 AR48082-05
Keywords: scleroderma, fibroblasts, microarrays, autoimmunity, collagen, gene expression, genetic regulatory element, molecular pathology, pathologic process, protein biosynthesis, fibrosis, gene mutation, genetic regulation, genetic transcription, reporter gene
Study Type: Basic
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 of 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 microarray 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. RNA's will be extracted from high collagen and low collagen producing cell populations. These RNA's 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: *EBNA-1 in Lupus* NIAID

P.I.: John B. Harley, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 5 R01 AI31584-12
Keywords: systemic lupus erythematosus, Epstein-Barr virus, Epstein Barr virus, B lymphocyte, autoimmune disorder, cytomegalovirus
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-lmmediate 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: *UCSF Autoimmunity Center of Excellence (ACE)* NIAID

P.I.: David Wofsy, M.D.
Institution: University of California, San Francisco
Grant No.: 5 U19 AI056388-03
Keywords: immunology, molecular biology, autoimmune diseases, clinical trials, immunotherapies, murine lupus, lupus nephritis, diabetes, multiple sclerosis, prevention, urologic disease
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 as described below: 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 costimulation 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 Costimulatory Signal (ACE)* NIAID
P.I.: Samia J. Khoury, M.D.
Institution: Brigham and Women's Hospital, Boston
Grant No.: 5 U19 AI046130-07
Keywords: autoimmune disease, prevention, autoimmune disorder, immunotherapy, clinical research
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 costimulatory 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 (ACE)* NIAID
P.I.: Ignacio Sanz, M.D.
Institution: University of Rochester, NY
Grant No.: 5 U19 AI056390-03
Keywords: diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, autoimmune diseases, pathogenesis, disease-specific autoantibodies
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 reagents 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 (ACE)* NIAID

P.I.: Eugene W. St. Clair, M.D.
Institution: Duke University, Durham, NC
Grant No.: 5 U19 AI056363-03
Keywords: B cell responses, immunotherapy, autoimmune diseases, lupus, arthritis
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 (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 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: *UAB Autoimmunity Center for Excellence (ACE)* NIAID

P.I.: Robert H. Carter, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 5 U19 AI056542-03
Keywords: translational therapies, immunology, autoimmune diseases, autoimmune disorder, autoimmunity, cooperative study, clinical research
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, San Francisco
Grant No.: 5 R03 EY014962-03
Keywords: Graves' disease, hyperthyroidism, autoantibodies, ophthalmopathy, animal model, autoimmune disease exophthalmic goiter, eye disorder, hormone receptor, hormone regulation /control mechanism, hyperthyroidism, thyrotropin
Study Type: Basic
Award: $151,500

The ophthalmopathy of Graves' disease is a disfiguring, sight threatening condition of unclear pathogenesis and no 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'-Iike animal model to investigate critical issues of Graves' disease as is Graves' ophthalmopathy as follows: 1. Graves' ophthalmopathy in the Graves'-Iike 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. c. Study the regulation of TSHR in orbital fibroblasts/preadipocytes. 2. Characterize TSHR antibodies in their relationship to Graves' ophthalmopathy.

▶ Title: *International Research Registry Network for Sjögren's Syndrome* NIDCR
P.I.: John S. Greenspan, Ph.D.
Troy Daniels, D.D.S., M.S.
Institution: University of California, San Francisco
Grant No.: N01 DE32636
Keywords: research registry, Sjogren's syndrome, international, dental/oral disease
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; and 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.

Infectious Diseases

▶ Title: *Seroprevalence/Incidence of Genital Herpes* FIC
P.I.: Edith Nakku-Joloba, Ph.D.
Institution: New Mulago Hospital, Kampala, Uganda
Grant No.: 5 R01 TW006672-03
Keywords: herpes, epidemiology, infectious diseases, prevention, rural health, vaccine related
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 i) To estimate the age and sex specific prevalence of Herpes simplex type 1 and 2. ii). To estimate the incidence of Herpes simplex type 1 and 2 in an inception cohort of HSV-2

negative persons in an urban population in Uganda and iii) to identify modifiable risk factors associated with Herpes simplex types 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 herpes simplex type 1 and 2. Incidence will be assessed in an inception cohort of HSV-2 negative persons by 6 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.

▶ Title: *Natural Antimicrobials Against Bacterial Vaginosis* NCCAM
P.I.: Mikhail Tchikindas, Ph.D.
Institution: Rutgers University, New Brunswick, NJ
Grant No.: 1 R21 AT002897-01
Keywords: lifespan, vaginosis, CAM, interdisciplinary research
Study Type: Basic
Award: $187,678

Bacterial vaginosis (BV) is a complex multi-microbial infection associated with the depletion of lactobacilli, the major flora of a healthy vagina and the overgrowth of Gardnerella vaginalis, Peptostreptococcus spp. and Prevotella bivia. BV may lead to premature labor. Endotoxins produced by the BV-associated bacteria cause serious brain/CNS damage in developing fetuses. Healthy vaginal Lactobacillus rhamnosus strain 160 produces an antimicrobial peptide, bacteriocin, designated as lactocin 160, which is active against BV associated microorganisms. He will examine their major hypothesis that this novel ribosomally-synthesized peptide is a potent antimicrobial agent for the prophylaxis and treatment of BV through the following three specific aims. He will determine lactocin 160's stability, safety, and spectrum of antimicrobial activity against BV associated vaginal pathogens. He expects lactocin 160 to be stable (alone and in combination with the selected natural antimicrobials), to have a broad range of antimicrobial activity against vaginal pathogens, and to be safe for human use (Specific Aim 1). Investigation of the mechanism of action by which lactocin 160 inhibits BV-associated microorganisms will lead to the understanding of the interaction between the cellular membrane and the peptide. He will determine whether one or both components of the Proton Motif Force are inhibited by lactocin 160 and if its activity is voltage-dependant, in other words, influenced by the growth phase of the pathogens. The investigator will find out if ATP in the bacteriocin-treated cells will be hydrolyzed intracellularly, or will leak off the cell (Specific Aim 2). Finally, he will prove that lactocin 160 has increased bactericidal activity against vaginal pathogens at low pH established specifically by lactic acid and when combined with synergistically acting natural and safe antimicrobials such as Zn lactate, saponin, and Polylysine, all of which have a mechanism of antimicrobial action different from lactocin 160 (Specific Aim 3). Our research will lead to a new approach for BV prophylaxis and treatment.

Menopause

▶ Title: *The Study of Women's Health Across the Nation (SWAN III)* NIA
P.I.: Kim Sutton-Tyrrell, Ph.D.
Institution: University of Pittsburgh
Grant No.: 5 U01 AG012553-11
Keywords: aging, hormones, menopause, minorities, reproductive aging, risk factors, AM, diabetes, hypertension, kidney-incontinence, behavioral and social science, cardiovascular
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%) 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 (two 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 follow-up. 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, Los Angeles
Grant No.: 5 U01 AT001653-03
Keywords: hormone therapy, soy protein, isoflavone-rich, soy protein, postmenopausal women, atherosclerosis, common carotid artery, estrogen, cancer, cardiovascular, CAM
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 soy 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 1 killer of postmenopausal women.

▶ Title: *Soy Isoflavones for Menopausal Vasomotor Symptoms* NCCAM

P.I.: Judith Ockene, Ph.D.
Institution: University of Massachusetts Medical School, Worcester
Grant No.: 1 R21 AT002522-01A1
Keywords: lifespan, reproductive life, menopause, CAM, clinical trial methods
Study Type: Clinical
Award: $324,190

Vasomotor symptoms (VMS), including hot flashes and night sweats, affect the majority of menopausal women. Since the results of the Women's Health Initiative were publicized, many women and their health care providers no longer wish to use hormone therapy for VMS. Soy isoflavones have been marketed for reducing VMS, but data are inconclusive as to their effectiveness. Although isoflavones are structurally similar to estrogen and thus bind to estrogen receptors, results from randomized controlled trials of both soy bods and supplements have been mixed. Given the pharmacokinetic characteristics of soy isoflavones, in particular the half-life (approximately 8 hours), dosing frequency may be critical to their effectiveness in reducing VMS. In addition, no intervention study of VMS has examined whether participants are equol producers. Equol, daidzein's active metabolite, may affect the efficacy of daidzein in reducing VMS intensity. The investigators propose to conduct a small pilot randomized placebo-controlled trial of 180 menopausal women with moderate to severe VMS to examine a range of doses (total daily dose of 100 mg/day and 200 mg/day) and three dosing frequencies (1, 2, and 3 times a day) of capsules containing the primary isoflavones found in soy (daidzein and genistein). Outcomes will include feasibility and preliminary dose evaluation. For feasibility aims they will: 1) assess their ability to recruit and retain participants; 2) measure adherence to capsules and to completing symptoms diaries; 3) modify and test a daily symptoms diary that is more complex than previously used; and 4) test the feasibility and utility of identifying equol producer status. For preliminary dose evaluation aims they will examine VMS as they relate to: 1) isoflavones by dose amount and dose frequency; 2) equol producer status; and 3) in a subgroup, steady state concentrations. These data will provide essential information for optimal study design, methods of data collection, and total daily dose and dosing frequency for a larger, more definitive randomized controlled trial.

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.: 5 R01 MH65871-04
Keywords: mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/alcohol abuse, clinical research, human subjects, behavioral and social science
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 U.S. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to (a) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); (b) test the direct associations between trauma and health outcomes; (c) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and (d) 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: *Pharmacogenomics and Pharmacogenetics Research Group* NIGMS
P.I.: Julio Licinio, M.D.
Institution: University of California, Los Angeles
Grant No.: 2 U01 GM061394-07
Keywords: depression, pharmacogenetics, treatment, Hispanics, Mexican-Americans
Study Type: Basic
Award: $50,000

This is a competitive renewal of our pharmacogenomic study of antidepressant treatment response in Mexican-Americans. We aim at identifying genetic substrates contributing to phenotypic variability in drug response in an ethnically defined, under-represented, and under-studied population. In this application we build on the infrastructure created in the current funding period to substantially enhance our ability to use the tools of contemporary genomics for prediction of antidepressant responses, by assembling a truly cross disciplinary structure that is greater than the sum of its parts. This will permit us to use a state-of-the-art pharmacogenomic strategy with three specific aims: 1) hypothesis generation, 2) hypothesis testing and 3) replication studies. Together with David Bentley and colleagues at the Sanger Institute we developed combined re-sequencing and genotyping strategies in a large number of candidate genes as a continuation of our existing collaboration. This represents an unparalleled opportunity to pursue a pathway-based approach while simultaneously leveraging a small effort on transcriptome and proteomics studies for gene/pathway discovery. Full-length direct sequencing of 100 genes in 96 individuals (48 best and 48 worst antidepressant responders) will maximize haplotype information in this under-

studied population. The results of this sequencing effort, in combination with the existing 105,632 SNPs deposited in dbSNP that are present in candidate genes in our pathways of interest, provide a rich source of polymorphisms for selection of candidates to be used for hypothesis generation. The polymorphisms with the strongest treatment response association will be selected for hypothesis testing. To further confirm findings emerging from hypothesis testing studies, a replication project has been planned with A. Serretti's group (Italy) that has the largest body of published data on antidepressant pharmacogenetics. Our initial funding has supported an ongoing prospective, double-blind trial of two antidepressants with collection of DNA samples from 300 depressed and 300 controls, community engagement, limited genotyping, and a bioinformatics core. We have developed productive collaborations within the PGRN and with other groups, nationally and internationally. All of our data to date have been deposited in PharmGKB. Our depositions into this public database will increase exponentially upon completion of ongoing and new collaborative studies with the Sanger Institute.

▶ Title: *Youth Suicide Prevention Using Community-Based, Participatory Research Methods to Design and Implement the Apache Youth Suicide Research and Prevention Program (NARCH-Indian Health Service)* NIGMS

P.I.: Maridde J. Craig
John Walkup, M.D.

Institution: White Mountain Apache Tribe, Whiteriver, AZ
Johns Hopkins University School of Medicine, Baltimore, MD

Grant No.: 1 S06 GM074004-01

Keywords: adolescent, Native American, mental health, prevention, suicide

Study Type: Clinical

Award: $25,000

The White Mountain Apache Tribe and Johns Hopkins Center for American Indian Health Native American Research Center in Health proposes to employ community-based, participatory research methods to design and implement the Apache Youth Suicide Research and Prevention Program for the White Mountain Apache Tribe in Whiteriver, Arizona. Rates of suicide among youth and young adults on the White Mountain Apache Reservation have been among the highest in the U.S. of any ethnic group in the past decade. The White Mountain Apache and Johns Hopkins have collaborated for more than 25 years in addressing the health and social priorities of the Tribe, with findings from past work generalized across Indian country and the world. To develop the Apache Youth Suicide Research and Prevention Program we will: (1) develop a surveillance and data collection system for the evaluation of suicidal behavior on the White Mountain Apache Reservation; (2) collect and analyze data from young suicide attempters (<19 years old) to identify key characteristics and determinants of suicidal behavior in this age group; (3) engage community experts in the development of a suicide prevention program that utilizes empirically supported prevention intervention strategies to target key determinants and characteristics in at risk Apache youth; and (4) develop a NIH grant proposal to test the efficacy of the Youth Suicide Prevention Program developed during the period of this award. The outcomes of this work will provide important models for other communities battling this increasing problem among adolescents and young adults.

Musculoskeletal Systems

▶ Title: *Osteo-Arthritis Initiative (OAI) -- Baltimore* NIAMS
P.I.: Marc Hochberg, M.D.
Institution: University of Maryland School of Medicine, Baltimore
Grant No.: N01-AR-2259
Keywords: biological markers, osteoarthritis, disease progression
Study Type: Clinical
Award: $67,033

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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: *Osteo-Arthritis Initiative (OAI)—Columbus* NIAMS
P.I.: Rebecca Jackson, M.D.
Institution: Ohio State University, Columbus
Grant No.: N01-AR-2261
Keywords: biological markers, osteoarthritis, disease progression
Study Type: Clinical
Award: $524,739

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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: *Osteo-Arthritis Initiative (OAI)—Pittsburgh* NIAMS
P.I.: C. Kent Kwoh, M.D.
Institution: University of Pittsburgh
Keywords: biological markers, osteoarthritis, disease progression
Grant No.: N01-AR-2260
Study Type: Clinical
Award: $208,228

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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 DE12872-05
Keywords: clinical trials, periodontitis, osteoporosis, dental/oral disease, estrogen osteoporosis, skeletal disorder, chemotherapy, tetracycline, bone density, bone metabolism
Study Type: Translational, Clinical
Award: $315,644

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: a) inhibit host-derived, tissue-destructive matrix metalloproteinases (MMPs), including collagenases, involved in bone resorption; and b) 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: a) alveolar bone crestal and subcrestal density (measured by computer-assisted densitometric image analysis) and linear alveolar crestal bone height; b) clinical periodontal measurements such as probing depth and relative clinical attachment level; and c) 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, Omaha, NE
Grant No.: 5 R01 AR048846-03
Keywords: osteoporosis, supplementation, menopause
Study Type: Clinical
Award: $75,000

Bone mineral is basically calcium phosphate, and both elements (Ca and P) are required for bone acquisition. Typical Ca intakes in the U.S. 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 one 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, Miami, FL
Grant No.: 5 R01 AR048932-03
Keywords: osteoporosis, menopause, hormone replacement therapy (HRT), prevention, estrogen
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 are 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.

Nutrition

▶ Title: *National Food and Nutrient Analysis Program (NFNAP)* NCI
Institution: Interagency Agreement between USDA and NIH
Grant No.: Y1-CN-5010-01
Keywords: nutrition, Latinos, Hispanics, nutrition database
Study Type: National Database
Award: $100,000

This is a joint NIH-USDA program to expand the current food and nutrient database to include foods commonly consumed by the Hispanic population in the United States. Additional partners include the FDA, the CDC and multiple Institutes and Centers across the NIH. The current database includes 1,000 foods and nutrients consumed by 80% of the population. Given the increasing Hispanic population in the U.S., there is an urgent need to expand the databases in include other foods and nutrients commonly consumed by this ethnic group.

▶ Title: *Botanical Supplements for Women's Health* NCCAM
P.I.: Norman R. Farnsworth, Ph.D.
Institution: University of Illinois at Chicago
Grant No.: 2 P50 AT000155-06
Keywords: menopause, botanicals, dietary supplements, CAM, estrogenic effects
Study Type: Basic, Clinical
Award: $100,000

Since the 1994 DSHEA mandate, botanical dietary supplements (BDSs) are continuously developing into safer and more effective preparations that aid U.S. public health. Since its establishment in 1999, our BOTANICAL CENTER has participated in this development by performing significant (bio-)chemical and clinical research on BDSs that are widely used to restore and/or maintain women's health. The focus of a renewed grant period will continue to be the alleviation of perimenopausal and premenstrual syndrome (PMS) symptoms. Linked to this focus is the central hypothesis that botanicals contain potent secondary plant metabolites that exhibit activities in estrogenic and major CNS (serotonin, GABA, dopamine, and opioid) systems. In close collaboration with the other projects of the CENTER, PROJECT 1 will (Aim 1) evaluate and prioritize select botanicals; (Aim 2) show that they contain phytoconstituents with the desired biological activities and profiles, in vitro and in vivo; isolate and structurally characterize these active principles by modern spectroscopical methods and use them to (Aim 3) standardize the botanicals. The long-term objective of this proposal is to prepare botanical extracts that are chemically and biologically standardized in terms of the bioactive secondary plant metabolite(s), and that are stable for human studies. Combining promising botanicals from the previous grant period with the results of preliminary studies, an initial selection of 12 plants plus two complex herbal mixtures will be evaluated. Primary extracts of a wide polarity range and their solvent partition fractions will be assayed in vitro and in vivo by PROJECTS 2+3, and prioritized using a scoring system that weighs hit numbers, grouping of potency, as well as strengths and concentration of activity. The botanicals with the highest rank will be scaled-up and subjected to an innovative bioassay-guided fractionation procedure (w/PROJECTS 2+3

and CORE B). The major active principles will be obtained through a sequential application of modern chromatography tailored to the specific characteristics of the extracts (HSCCC, Gel/Resin-CC). Modern qualitative and quantitative spectroscopic analysis (1/2D and selective NMR, qNMR, hyphenated MS) will lead to the identification of structures of the major active principles, which ultimately lays the foundation for chemical and biological standardization. Prioritized botanicals will be fully developed into standardized products. Hops will be evaluated in a Phase I clinical study in PROJECT 4.

Obesity/Overweight

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise Weight Reduction for Incontinence Network (WIN)* NIDDK

P.I.: Deborah G. Grady, M.D.
Institution: University of California, San Francisco
Grant No.: 5U01 DK860-03
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $100,000

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 and over 65% 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.

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise Weight Reduction for Incontinence Network (WIN)* NIDDK

P.I.: Rena R. Wing, Ph.D.
Institution: Miriam Hospital, Providence, RI
Grant No.: 5 U01 DK67861-03
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $75,000

The aims of the study are 1) to determine whether weight loss will reduce the frequency of urinary incontinence in overweight women with incontinence and 2) to determine whether a motivationally-based program will improve weight loss maintenance compared to a skill-based maintenance program.

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise Weight Reduction for Incontinence Network (WIN)* NIDDK

P.I.: Frank Franklin, M.D., Ph.D.
Institution: University of Alabama, Birmingham
Grant No.: 5 U01 DK067862-03
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $75,000

The specific aims of this study, are to determine whether randomization to a behavioral weight control program results in greater reductions in frequency of incontinence episodes at 6 months compared to usual care and to identify women who are most likely to experience improved incontinence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed), have not changed or been modified since funding. The study protocol and interventions have been designed to support the aims of this study. The study design is a multicenter randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month intensive behavioral weight reduction program or usual care (no weight reduction intervention) and followed for 18 months. After completing the intensive weight reduction program, a second randomization will be done to test whether an enhanced weight maintenance program results in superior long-term weight loss through 18 months compared to a standard maintenance program. In a subgroup of 100 women, we will perform standard urodynamic studies to allow us to evaluate the mechanism by which weight loss improves incontinence.

▶ Title: *Health Outcomes of Weight-Loss: Data Coordinating Center (SHOW/Look AHEAD)* NIDDK

P.I.: Mark A. Espeland, Ph.D.
Institution: Wake Forest University, Winston-Salem, NC
Grant No.: 5 U01 DK57136-07
Keywords: obesity, health disparities, type 2 diabetes, clinical trials, sex differences, weight loss, physical activity, CVD risk factors, behavioral interventions, health promotion, disease prevention
Study Type: Randomized Clinical Trial
Award: $100,000

This application describes plans by an experienced group of investigators and staff at the Wake Forest University School of Medicine (WFU) to serve as the Coordinating Center (CoC) for the Study of Health Outcomes of Weight-Loss (SHOW). SHOW is a multicenter randomized trial designed to test whether weight loss interventions can reduce the progression of carotid atherosclerosis and other health outcomes in a cohort of 6000 obese type 2 diabetics. Participants will be randomized to one of 3 intervention arms: intensive lifestyle intervention (diet and exercise), intensive lifestyle intervention plus pharmacotherapy, or community control. The primary outcome is carotid intimamedial thickness. Secondary outcomes include cardiovascular (CV) and cerebrovascular events and death, CV risk factors, and glycemic control. Participants will be recruited over a 3-year period with 4-7 years of intervention and follow-up. WFU plans to operate the CoC for the SHOW trial. In that role, we will provide expert statistical support for sample size, data analyses and interpretation; collaborate in the design of SHOW and provide all supporting study documents including manuals and data collection forms; design and implement a web-based data management system; plan and support recruitment efforts in the 15 clinics; develop and monitor all quality control efforts; monitor recruitment, retention, the implementation of the intervention, and adherence; subcontract with all Core Facilities (e.g., central laboratory); train and certify staff, perform study administrative duties; and participate in paper writing.

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.: 5 U10 EY13626-04
Keywords: blindness, quality of life, aging, Caucasian women, diabetes, eye disease and disorders of vision, macular degeneration
Study Type: Epidemiologic (Case-Control)
Award: $230,000

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

▶ Title: *Estrogen Receptors and Maintenance of Lens Transparency* NEI
P.I.: Vicki L. Davis, Ph.D.
Institution: Cedars-Sinai Medical Center, Los Angeles
Grant No.: 5 R01 EY014600-03
Keywords: ophthalmic diseases, aging, estrogen, cataract, estrogen receptor, lens, receptor expression, eye disorder chemotherapy, eye pharmacology
Study Type: Basic
Award: $132,549

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 2 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? 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 2 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 or 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: *Hormonal Cycles in Women: Effects on TMD Pain and Symptoms* NIDCR
P.I.: Linda Leresche, Sc.D.
Institution: University of Washington
Grant No.: 5 R01 DE016212-02
Keywords: TMJ, pain control, estrogen, depression, mental health, mind and body
Study Type: Translational
Award: $150,000

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: *Pain Management in Temporomandibular Joint Disorders* NIDCR
P.I.: Jennifer Haythornthwaite, Ph.D.
Institution: Johns Hopkins University, Baltimore, MD
Grant No.: 5 R01 DE13906-05
Keywords: TMD, pain control, behavioral interventions, neurosciences research, dental/oral disease
Study Type: Clinical, Behavioral
Award: $269,127

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

▶ Title: *Trigeminal Pain Mechanisms and Control: Mechanisms of Pain Caused by Disruption of Microtubules* NIDCR
P.I.: Jon D. Levine, Ph.D.
Institution: University of California, San Francisco
Grant No.: 5 P01 DE08973-15
Keywords: pain control mechanism, orofacial neuropathies, neurosciences research, dental/oral disease, neurodegenerative
Study Type: Basic
Award: $168,176

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 re-

duce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

▶ Title: *Imaging the Cognitive Modulation of Pain in Fibromyalgia* NIAMS
P.I.: Dane B. Cook, Ph.D.
Institution: VA Medical Center, East Orange, NJ
Grant No.: 1 R01 AR050969-01A1
Keywords: chronic pain, fibromyalgia, brain imaging, rheumatoid arthritis
Study Type: Clinical
Award: $250,000

Fibromyalgia (FM) is a disabling disorder characterized by widespread medically unexplained pain. A diagnosis of FM is accompanied by a poor prognosis and less than half of all FM patients experience adequate pain relief. FM patients are often left under treated, resulting in greater functional disability and increased health care utilization. Research aimed at uncovering mechanisms of unexplained pain in FM is needed to guide potential treatment approaches and better understand the pathophysiology of this disorder. Brain imaging data collected in our laboratory have demonstrated augmented fMRI responses to both nonpainful and painful heat, and support the emerging view that abnormalities in central nociceptive processes act to maintain FM pain. However, cognitive processes such as anticipation and attention could also affect brain responses and are known to affect chronic pain outcomes. The broad objectives are to further our understanding of unexplained musculoskeletal pain in FM. fMRI is an objective measure of nociceptive processing, sensitive to sensory and cognitive manipulations. Thus, the specific aims of the project are to: (1) determine whether augmented central processing is unique to FM or is a consequence of chronic pain by comparing FM patients to rheumatoid arthritis patients (RA); (2) determine the influence of pain anticipation on fMRI responses to non-painful stimuli in FM patients compared to healthy and RA controls, and (3) determine the influence of attention to pain on central processing of painful stimuli in FM patients compared to healthy and RA controls. To manipulate anticipation of pain, subjects will be randomly assigned to "pain" and "no pain" conditions. To manipulate attention to pain, subjects will perform the Stroop color word task while receiving either painful or non-painful heat stimuli. The study will be conducted on two separate days. Day one will be conducted in a simulated MRI unit for psychophysical analysis of pain and performance of the Stroop. Day two will consist of functional brain imaging (fMRI) while the subjects receive either nonpainful or painful heat stimuli and perform the Stroop. The investigators hypothesize that FM is a unique chronic pain disorder that involves dysregulated processing of sensory stimuli and that augmented brain responses will not be affected by manipulations of anticipation and attention. This will be a first important step towards understanding the mechanisms of unexplained muscle pain in FM.

Physical Activity

▶ Title: *Social Cognitive Theory and Physical Activity after Endometrial Cancer Intervention* NCI
P.I.: Karen M. Basen-Engquist, Ph.D.
Institution: University of Texas MD Anderson Cancer Center
Grant No.: 5 R01 CA109919-02
Keywords: physical activity, endometrial cancer, social cognitive theory
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 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 six-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every two 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.: Barry M. Popkin, Ph.D.
Institution: University of North Carolina, Chapel Hill
Grant No.: 5 R01 CA109831-02
Keywords: physical activity, physical environment, cardiovascular disease, race/ethnic differentials, coronary heart disease, prevention
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 18-30 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 life-cycle. 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.: Angela Bryan, Ph.D.
Institution: University of Colorado, Boulder
Grant No.: 5 R01 CA109858-02
Keywords: exercise behavior, cancer, cardiovascular disease, type II diabetes mellitus, physical activity, race/ethnicity, behavioral and social science, nutrition, prevention
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 II diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30% 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% of the U.S. population do not get the recommended amount of physical activity as defined by 30 minutes of moderate intensity physical activity 5 or more days per week, and 40% 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) That 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: *Angiogenesis and Mechanisms of Exercise Training* NHLBI
P.I.: Brian H. Annex, M.D.
Institution: Duke University Medical Center, Durham, NC
Grant No.: 5 R01 HL075752-03
Keywords: artery, atherosclerosis, exercise, behavioral and social science, cardiovascular, chronic pain conditions
Study Type: Clinical
Award: $100,000

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5% of the US 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.

Reproductive Health/Developmental Biology

▶ Title: *ORWH-NICHD Leiomyoma Tissue Bank* NICHD
P.I.: James Segars, M.D.
Institution: NICHD, Bethesda, MD
Grant No.: 1 Z01 HD008737-05
Keywords: minority health, African American women, etiology, uterine fibroids (leiomyoma), reproductive health, benign tumors, gynecology
Award: $93,000

Health of 30-50% of women in the U.S. is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

▶ Title: *Protein Tyrosine Kinases in Leiomyomata Uteri* NICHD
P.I.: Jean Wang, Ph.D.
Institution: University of California, San Diego
Grant No.: 5 R01 HD046225-03
Keywords: protein tyrosine kinases, tumor growth, uterine myometrium, leiomyoma
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 and Women's Hospital, Boston
Grant No.: 5 R01 HD046226-03
Keywords: uterine fibroids, cytogenetic, uterine leiomyomata, African American women, genetics
Study Type: Translational
Award: $75,000

Although the majority of uterine leiomyomata are karyotypically normal, cytogenetic abnormalities are found in 25-40% 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.: 5 R01 HD046228-03
Keywords: estrogen receptor, immune response, recombinant adenovirus, selective estrogen receptor modulator, leiomyoma, fibroid tumors
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 application 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
Grant No.: 5 R01 HD046282-03
Keywords: leiomyoma, tumor suppressor gene, estrogen receptor signaling, fibroid tumors, genetics
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
Grant No.: 5 R01 HD046251-03
Keywords: estradiol, extracellular matrix, gene interactions, smooth muscle, fibroid tumors, estrogen
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
Grant No.: 5 R01 HD046227-03
Keywords: smooth muscle, obesity, hypertension, African American women, fibroid tumors
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
Grant No.: 5 R01 HD046249-03
Keywords: cytoxic gene therapy, dietary, estrogen alpha-receptor antagonist, gonadotropin releasing hormone agonist, leiomyoma, fibroid tumors
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
Grant No.: 5 R01 HD046260-03
Keywords: aromatase expression, estrogen biosynthesis, myometrium, fibroid tumors
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: *Intermediate Outcomes of Hysterectomy and Alternatives* NIEHS

P.I.: Miriam Kuppermann, Ph.D.
Institution: University of California, San Francisco
Grant No.: 5 R01 HS11657-04
Keywords: hysterectomy, quality of life, pelvic pain, endometriosis, fibroid tumors, chronic pain conditions, decision making, hysterectomy, uterus disorder, chronic pain, endometriosis, leiomyoma, urinary incontinence, women's health
Study Type: Outcomes 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 to 1) determine whether and how intermediate-term (4-8 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. 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 four years of follow-up data on over 976 women. The increased sample at four 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 40?s to menopause, including intermediate-term, face this decision, 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 decision making 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: *Pregnancy and Drug Metabolizing Enzymes and Transporters (OPRU)* NICHD
P.I.: Steve N. Caritis, M.D.
Institution: Magee-Womens Research Institute, Pittsburgh, PA
Grant No.: 5 U10 HD047905-02
Keywords: women, pregnancy, drugs, drug metabolism and transport, clinical trials, genetics
Study Type: Basic, Clinical
Award: $50,000

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 8000 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 (OPRU)* NICHD
P.I.: Menachem Miodovnik, M.D.
Institution: Georgetown University, Washington, DC
Grant No.: 5 U10 HD047890-02
Keywords: women, pregnancy, drugs, epilepsy, anticonvulsants, clinical trials, genetics
Study Type: Basic, Clinical
Award: $50,000

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, 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 (GU) (lead agency) and George Washington University (GWU) with the clinical strengths of MedStar Health (Washington Hospital Center [WHC] and Georgetown University Hospital [GUH]), GWU Hospital, and Children's National Medical Center (CNMC). 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 multi-center 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: *UW Obstetric-Fetal Pharmacology Research Unit (OPRU)* NICHD
P.I.: Mary F. Hebert, Pharm.D.
Institution: University of Washington
Grant No.: 5 U10 HD047892-02
Keywords: women, pregnancy, drugs, diabetes, anti-diabetes drugs, drug metabolism, clinical trials, genetics
Study Type: Basic, Clinical
Award: $50,000

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 following 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 (OPRU)* NICHD
P.I.: Gary D. Hankins, M.D.
Institution: University of Texas Medical Branch, Galveston
Grant No.: 5 U10 HD047891-02
Keywords: women, pregnancy, drugs, diabetes, anti-diabetes drugs, clinical trials
Study Type: Basic, Clinical
Award: $50,000

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 (SNPRC) 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 RFA 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: *Impact of Sex Differences and Pregnancy in Drug Disposition–Adverse Effects* NICHD
P.I.: Menachem Miodovnik, M.D.
Institution: Georgetown University, Washington, DC
Grant No.: 5 U10 HD047890-02S1
Keywords: sex differences, drug disposition, pharmacology, obstetrics
Study Type: Literature Review, Ancillary Study
Award: $75,000

Men and women differ in response to drug treatment. Anatomical, physiological, and molecular differences between the sexes account for differences in clinical therapeutics. To design safe and effective drug treatment, it is essential to understand how men and women differ in disposition of and response to drugs. Additionally, it is important to understand how sex differences influences disposition and responses to drugs in pregnancy. This project would critically evaluate adverse effects of drugs in men, women and during pregnancy. The study would be completed in a year. It would primarily be a literature review pulling together adverse effects data, though the investigator would also use the FDA adverse events files and explore using the similar files in the WHO adverse events system housed in Uppsala, Sweden.

▶ Title: *Gestational Hypothyroidism: Is the Current Treatment Regimen Adequate? Single Dose and Steady State Pharmacokinetics Based on State-of-the-Art Analytical Methods* NICHD
P.I.: Menachem Miodovnik, M.D.
Institution: Georgetown University, Washington, DC
Grant No.: 5 U10 HD047890-02S2
Keywords: hypothyroidism, pregnancy, pharmacokinetics
Study Type: Clinical, Ancillary Study
Award: $25,000

Hypothyroidism during pregnancy present clinicians with a unique challenge, optimal dosing regimens developed and validated for non-pregnant women cannot be extrapolated to pregnancy. Hypothyroidism in pregnancy is associated with higher rates of complications such as spontaneous abortions, preeclampsia, stillbirth, and prematurity. Low thyroid hormone (TH), especially thyroxine (T4), is also associated with adverse effects on fetal growth and development and is critical for normal brain development. Because the fetal thyroid is not fully formed until gestational week (GW) 16, during the first half of pregnancy the fetus totally depends on maternal supply of TH. After GW 16, the fetus continues to partially rely on maternal thyroid hormone supply until delivery. Hypothyroid mothers who are not appropriately supplemented will not provide adequate thyroxin to the baby. Therefore, early identification of hypothyroidism in pregnant women is extremely important. Recent studies have shown that standard immunoassays (IAs) consistently overestimate thyroid hormone concentrations during pregnancy. Using current generally accepted IA methods, it is estimated that as many as 50 percent of pregnant hypothyroid women could be missed - which could result in neurobehavioral deficits in thousands of babies. There is no evidence-based treatment of hypothyroidism in pregnancy. Currently patient treatment is determined by thyroid stimulating hormone (TSH) levels. For appropriate LT4 supplementation of

hypothyroid women in pregnancy, thyroid hormone measurements should be based on state of the art detection methods. The investigators' objectives are to estimate LT4 PK parameters in pregnant women already receiving LT4 to treat their hypothyroidism; to compare 1st to 3rd trimester TH PK in LT4-treated hypothyroid women, and compare these to same subject post-partum levels, and to PK during lactation; to measure, in LT4-treated women, FT4, T4 and T3 trough steady state levels on gestation weeks 8-10, 22-24, 32; and single dose studies using stable isotopes.

▶ Title: *Development and Differentiation in Reproductive Axis* NICHD
Cooperative Reproductive Sciences Research at Minority Institutions
P.I.: David R. Mann, Ph.D.
Tony M. Plant, Ph.D.
Institution: Morehouse School of Medicine, Atlanta
University of Pittsburgh
Grant No.: 5 U54 HD41749-05
Keywords: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation
Study Type: Basic, 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. Grant No. 4--1U54HD41749-010004 (SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

▶ 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
Grant No.: 5 U54 HD041748-03
Keywords: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, genetics, minority health
Study Type: Basic, 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: *MMC/PSU Cooperative Center for Research in Reproduction* NICHD
P.I.: Ponjola Coney, M.D.
Institution: Meharry Medical College, Memphis, TN
Grant No.: 5 U54 HD044315-03
Keywords: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, fibroid tumors, estrogen
Study Type: Basic, 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: (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: *Mechanisms of aPL Antibody-Induced Pregnancy Loss* NIAMS
P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 2 R01 AR38889-14
Keywords: antiphospholipid antibody syndrome, autoantibodies, autoimmune disease, miscarriage, complement
Study Type: Basic, Interdisciplinary
Award: $100,000

The antiphospholipid syndrome (APS), characterized by thrombosis and pregnancy loss that occurs in the presence of antiphospholipid (aPL) antibodies, is a leading cause of miscarriage and maternal and fetal morbidity. Pregnancy complications in women with APS include fetal death, preeclampsia, and intrauterine growth restriction (IUGR). The pathogenic mechanisms that lead to injury in vivo are incompletely understood and the therapy for pregnant women with APS is only partially successful. Our studies in a murine model of APS, induced by passive transfer of human Apl antibodies, indicate that complement activation plays an essential and causative role in fetal loss and growth restriction. In addition, treatment with heparin, the standard therapy for pregnant patients with APS, prevents complement activation and protects mice from pregnancy complications induced by aPL antibodies, while anticoagulants that do not inhibit complement do not protect pregnancies. These studies indicate that APS is an inflammatory disease and, they suggest that complement inhibitory therapy might be an effective treatment. Our overall goals are to use the murine model of APS to determine how complement is activated, which complement products mediate the clinical complications associated with aPL antibodies, and the

relative role of complement activation within the overall inflammatory cascade. In addition, we propose to test the hypothesis that activation of complement at the maternal-fetal interface plays an etiologic role in IUGR. The aims are: Aim 1. To determine which complement components and receptors are necessary or sufficient to mediate aPL antibody-induced placental injury, fetal loss and/or IUGR. (a) To identify the pathways that initiate complement activation and lead(s) to complement deposition in deciduas and poor pregnancy outcomes; (b) To identify the complement activation products and receptors that mediate fetal injury; (c) To assess the role of murine complement regulatory proteins in the control of local complement activation. Aim 2. To define the role of aPL antibody-mediated complement activation within the overall inflammatory cascade in order to identify complement-dependent vs. complement-independent mechanisms, (a) To define the contribution of FcgR to aPL antibody-mediated injury; (b) To define the cellular and cytokine mediators which contribute to complement activation in deciduas, to IUGR and to fetal loss. The proposed study, together with their ongoing work to define the role of complement and cytokines in pregnancy complications in APS patients, will provide insights into the mechanisms by which complement induces disease and define targets for interventions to prevent aPL antibody-associated fetal demise and IUGR. Additionally, understanding how aPL antibodies "cause" pregnancy loss may translate into new concepts about maternal-fetal tolerance and miscarriages in general and benefit women with non-aPL-related pregnancy complications.

▶ Title: *American Indian Women and Childbearing Experiences* NINR

P.I.: Janelle F. Sagmiller-Palacios, B.S.N.
Institution: University of California, San Francisco
Grant No.: 1 F31 NR009627-01
Keywords: American Indian, maternal child health, childbearing, vulnerable populations, adolescents, minority
Study Type: Clinical
Award: $41,527

Early childbearing is a common and poorly understood event among the American Indian population. In 2002 American Indian early childbearing rates of 53.8 per 1,000 live births were higher than total U.S. rates of (42.9) and White rates of (28.6). Childbearing American Indian women typically have significantly worse maternal/child outcomes compared to other groups. This pilot study is designed to explore, retrospectively, the early childbearing (prior to 18 years of age) experiences of American Indian women who currently live in urban areas. This interpretive study seeks to understand the lived experiences of early childbearing for American Indian women. Early childbearing experiences to be examined are: 1) decisions for bearing children early in life; 2) cultural values and beliefs associated with early childbearing; and 3) support structures and barriers. Twenty women will be drawn from the Native American Health Centers located in Oakland and San Francisco, California. Audiotapes will be transcribed verbatim. This study addresses an important area of research related to understanding the needs of vulnerable populations. Future work will target identified issues from this study, enabling American Indian communities to promote healthy maternal and child outcomes and facilitate postponement of early childbearing.

Violence

▶ Title: *Impact of Domestic Violence on Cancer Treatment.* NCI

P.I.: Jeanne E. Hathaway, M.D.
Institution: Harvard University, School of Public Health, Cambridge, MA
Grant No.: 1 R03 CA119198-01A1
Keywords: violence, domestic, against women, cancer, behavioral research, minority women
Study Type Clinical
Award: $7,936

Domestic violence (DV) is experienced by one to three million Americans annually and has been shown to disproportionately impact the health and health care access of women. DV has also been associated with cervical neoplasia and key risk factors for cancer, including smoking and drinking. Anecdotal reports further indicate that DV may delay the diagnosis of cancer, interfere with cancer treatment, and negatively impact women's health during cancer treatment. Despite this evidence, no research has focused on the relationship between DV and cancer. Research design and specific aims: This exploratory study aims to conduct in-depth interviews with a culturally diverse sample of individuals who have experienced abuse by an intimate partner while in cancer treatment (n = 32). Interviews will be semi-structured and conducted in English or Spanish. Interviews will focus on the effects of DV on cancer development, identification, and treatment, and participants' opinions as to how oncology and other health care providers can best identify, support, and protect patients facing both cancer and DV. Subjects will be recruited through oncology centers, a hospital-based DV program, cancer resource centers, local newspapers, and flyers posted in participating hospitals and the community. Interviews will be analyzed using grounded theory methodology. Contribution and long-term objective: This will be the first known study to explore the impact of DV on any chronic disease, including cancer. Study findings will be used in educating oncology and other health care providers about the impact of DV on cancer treatment and formulating efforts to address DV among oncology patients. Findings from this study may ultimately contribute towards improved health care and safety of individuals facing both cancer and domestic violence.

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 57-84 will be followed longitudinally in two waves over five 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; 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.

▶ Title: *California Native American Research Center for Health (NARCH)* IHS

P.I.: Deven R. Parlikar, M.B.A.
Mario Garrett, Ph.D.

Institution: Indian Health Council
San Diego State University

Grant No.: 5 S06 GM074084-02

Keywords: Native American, care-giving, elderly

Study Type: Clinical

Award: $75,000

The California Native American Research Center for Health (CA-NARCH) is a partnership of tribal and university organizations committed to working together to reduce health disparities in Native American populations and to increase the number of Native American (NA) scientists and health professionals. The Southern California Tribal community, which ranges from the California-Mexico border to Riverside County with 17 reservations, is the service area of the CA-NARCH project. The Indian Health Council, located in North San Diego County, is the lead agency, and houses the core administrative/research center. The university partners are San Diego State University and the University of California, San Diego. The goals of the CA-NARCH are to (1) develop a cadre of NA scientists and health professionals engaged in biomedical, clinical, behavioral, and health services research who will be competitive in securing NIH and AHRQ funding; (2) increase the capacity of both research institutions and NA organizations to work in partnership to reduce distrust by NA communities toward investigators in research; and (3) encourage competitive research linked to the health priorities of the native organizations and to reduce health disparities. Goal 1 will be accomplished by further implementing student and faculty development programs. The core administrative/research center will continue to focus on Goal 2. The CA-NARCH has begun the process of developing new research Initiatives to address Goal 3. In addition, this application includes two specific research projects and a pilot project proposed by one of our Native American faculty members: 1) examination of the association of Type II diabetes with active and passive tobacco exposure in Southern California Native Americans; (2) examination of perceived burden and resilience among caregivers of frail Native American elders in San Diego County; and (3) examination of alcohol consumption patterns and knowledge of fetal alcohol syndrome among Native American women of childbearing age.

▶ Title: *Caregivers' Strengths-Skills: Managing Older CA Patients* NCI
P.I.: Victoria H. Raveis, Ph.D.
Institution: Columbia University Health Sciences, New York, NY
Grant No.: 5 R01 CA115315-02
Keywords: symptom management, palliative care, behavioral intervention, low income, caregiving, quality of life, depression
Study Type: Clinical
Award: $48,825

We propose to implement and evaluate the efficacy of a short-term problem-solving skills training program for familial caregivers to lower income older (60+) post-treatment cancer patients. The goal of the intervention is to equip family caregivers with problem-solving skills and knowledge that will provide them with a more adaptive means of attending to any symptoms their elderly relative may be experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the post-treatment period, we propose that we will be able to impact patients' health related quality of life, by fostering enhanced symptom recognition, improved symptom control, advocacy with health professionals, and adherence to symptom management options. Familial caregivers to older cancer patients who have completed active treatment will be accrued from Community/Migrant Health Centers (C/MHCs). Caregivers and patients will be followed for ten months. The specific aims are to:

(1) Deliver a brief problem-solving training program with regard to symptom management ("Problem-solving") to enhance caregiver skills (i.e., perceived self-efficacy, social problem-solving and communication) of familial caregivers to older post-treatment cancer patients.

(2) Evaluate the efficacy of problem-solving in enhancing caregiver skills, relative to participating in a caregiver support group ("Support"): (a) Assess short- and long-term change in caregiver skills reported by caregivers assigned to either the Problem-solving condition or the Support condition; and, (b) Compare change reported by caregivers in the Problem-solving condition, relative to reports by those in the Support condition;

(3) Assess the impact of change in caregiver skills on: (a) Change in patients' symptomology and physical functioning, depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with care ("patient outcomes"); (b) Change in caregivers' depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with patient care ("caregiver outcomes").

(4) Disseminate information that informs family training in palliation and symptom control to participating C/MHCs and other C/MHCs serving these populations, contingent on demonstrating beneficial program outcomes.

Alcohol and Other Substance Abuse

▶ Title: *Sex Differences in Opioid Analgesia* NIDA
P.I.: Anne Z. Murphy, Ph.D.
Institution: University of Maryland, Baltimore
Grant No.: 5 R01 DA16272-05
Keywords: opioids, gender, pain, analgesia
Study Type: Clinical
Award: $48,825

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 animals models of acute

pain, the effective dose of morphine is approximately 5-lOx 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 gray (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. Our 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. Our 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. In summary, 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: *Reducing Alcohol and Risks Among Young Females* NIAAA
P.I.: Lydia N. O'Donnell, Ph.D.
Institution: Education Development Center, Newton, MA
Grant No.: 5 R01 AA014515-04
Keywords: alcohol, African American, Latina adolescent females, HIV/ AIDS, alcoholism, basic and social science, infectious diseases, minority health
Study Type: Clinical
Award: $144,500

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% 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 under-addressed 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 (PM) shown to influence adolescent risk behavior will be targeted: parental monitoring (P-PM), household rule setting (HR-PM), and communication (C-PM).

▶ Title: *Vulnerability to Drug Abuse and Treatment Efficacy: Animal Models* NIDA
P.I.: Marilyn Carroll, Ph.D.
Institution: University of Minnesota
Grant No.: 1 R01 DA003240-23
Keywords: hormones, puberty, substance abuse, stress, girls
Study Type: Basic
Award: $306,356

The overarching goal of this research is to identify vulnerability factors for psycho-stimulant addiction (specifically cocaine and methamphetamine) and to develop behavioral and pharmacological treatments for this disorder. Over the past several years, this investigator has emerged as the preeminent drug abuse

researcher studying sex differences in drug abuse in animal models. Thus, underlying this proposed research is analysis of data by sex and the study of hormonal influences on outcomes. In Specific Aim 1, the role of sex and sex hormones on the acquisition, escalation, and reinstatement of drug seeking/taking will be evaluated, including the influence of progesterone, estrogen, and selective estrogen receptor agonists. Assessment of the role of hormonal variables will include evaluating drug taking before, during and after pregnancy/weaning. Specific Aim 2 focuses on identification of behavioral methods for reducing the escalation and reinstatement (i.e., relapse) of drug abuse in vulnerable phenotypes as determined by impulsivity, wheel running and sucrose intake, all of which in prior research have been demonstrated to be predictive of drug abuse vulnerability. Finally, Specific Aim 3 will examine the effects of the GABA-B agonist baclofen and progesterone on cocaine and methamphetamine taking/seeking. Again, in both Specific Aims 2 and 3, sex differences in outcomes will be assessed.

▶ Title: *Functionality of the Opioid System during Adolescent Development Across Genders* NIDA

P.I.: Shoshana Eitan, Ph.D.
Institution: Texas A and M University
Grant No.: 1 R03 DA022402-01
Keywords: post-traumatic stress disorder (PTSD), substance use disorder (SUD), HIV risk behaviors, impulsivity, sexual abuse, minorities, African-American, Hispanic
Study Type: Basic
Award: $65,475

The goal of this research is to broaden the understanding of the opioid system during adolescence with respect to function and ontogenesis. Moreover, this research is designed to build a foundation for future discovery of the molecular mechanisms underlying such ontogenesis and functionality. Specifically, the first aim will examine age and gender differences in the effects of acute morphine exposure on levels of cellular signaling molecule activation and immediate early gene expression in brain areas of interest to NIDA. The second aim will investigate age and gender differences in sensitivity to developing morphine sensitization and the possible molecular mechanism underlying these differences. The proposed work is novel in that it also tries to determine potential social conditions and how they interact/influence the opioid system and whether these manipulations will render the organism more or less vulnerable to the behavioral and cellular effects of morphine exposure. More so, is the great undertaking, and much needed, assessment of gender differences. The major strength of this application is that it combines neurochemical and behavioral approaches to study the opioid system during adolescent development. The research focuses on gender differences during the adolescent period, a time of considerable vulnerability for the initiation of drug abuse. Its approach is multidisciplinary and includes multiple levels of analysis in its attempt to understand gender differences in developing morphine sensitization.

Cancer

▶ Title: *Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines* NCI
P.I.: Allan Hildesheim, Ph.D.
Douglas R. Lowy, M.D.
Institution: National Cancer Institute, Bethesda, MD
Grant No.: 1 Z01 CP10177-06
Keywords: human papillomavirus, cervical cancer, vaccine development, STDs
Study Type: Clinical
Award: $1,100,000

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, 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 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 12,000-15,000 women expected to participate. Eligible women who agree to participate will be administered 3 doses of either a control vaccine or the HPV 16/18 VLP vaccine over a six month period and will be followed for four 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: *Pharmacogenetics of the Endocrine Treatment of Breast Cancer* NIGMS
P.I.: David A. Flockhart, M.D., Ph.D.
Institution: Indiana University-Purdue University at Indianapolis, IN
Grant No.: 5 U01 GM061373-07
Keywords: pharmacogenetics, breast cancer, translational research, tamoxifen (TAM)
Study Type: Basic, Translational
Award: $244,125

Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer, and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but which drug is best for each woman remains unclear. Our work in the first cycle of the Pharmacogenetics Research Network identified, through a series of laboratory and clinical studies, new genetic patterns that predict effects of the estrogen receptor modulator tamoxifen. We now propose to build on these data to examine the influence of an extended series of candidate genes on the effects of the aromatase inhibitor class of drugs and to refine the genetic signatures that predict tamoxifen effects. Our work will involve the following broad specific aims: 1) To identify common genetic variants of the human estrogen receptors and important nuclear coactivators and repressers of these receptors using a combined bioinformatic and direct sequencing approach; 2) To test the hypothesis that these variants alter gene expression or function using in vitro assays; 3) To test the contribution of variants identified during specific aim 1 and 2 to tamoxifen response in the clinical trial of tamoxifen pharmacogenetics already conducted. 4) To characterize the involvement of genetically polymorphic drug metabolizing enzymes in the human metabolism of the available aromatase inhibitors: letrozole, exemestane and anastrozole in vitro. 5) To test the hypothesis that variants in candidate genes identified

in aims 1-4 are associated with well curated phenotypic outcomes, including estrogen metabolite concentrations, pharmacokinetics, hot flashes, breast density, bone metabolism and serum lipid subfractions in breast cancer patients receiving anastrozole, exemestane and letrozole. The results of this proposal will generate new information that, linked with our novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools key to optimizing drug selection for women with breast cancer and to our understanding of the mechanisms of estrogen action.

▶ Title: *Patient-Centered Communication During Chemotherapy* NCI

P.I.: Douglas M. Post, Ph.D.
Institution: Ohio State University
Grant No.: 5 R21 CA115388-02
Keywords: symptom management, palliative care, pain, depression, fatigue, breast cancer, behavioral intervention
Study Type: Clinical
Award: $48,825

Pain, depression, and fatigue are among the most common disease and treatment-related symptoms experienced by cancer patients. Studies have indicated that communication problems between cancer patients and clinicians are a major barrier to the effective management of these symptoms. This project is designed to address this important problem through the development and evaluation of a PDA-based patient communication intervention for breast cancer patients undergoing chemotherapy treatment. The intervention will be comprised of two integrated components: symptom monitoring and tailored patient communication training. Patients will be asked to complete fatigue, depression, and pain inventories on a PDA at the beginning of chemotherapy and once per week through the completion of treatment. On the day prior to an appointment for chemotherapy treatment, a summary of fatigue, depression, and pain scores will be integrated with a tailored patient communication skills training program and displayed on the PDA for patient viewing. Patients will be taught, through role modeling, how to effectively communicate the types of symptoms they have experienced between treatments. They will also be encouraged to bring the PDA with their symptom summaries to each chemotherapy visit and to share this information with their health care provider. Year one of the project will primarily be devoted to the development and usability testing of the intervention. A feasibility trial will be conducted during the second year. Fifty patients with breast cancer will be recruited into the trial at the start of their chemotherapy treatment. A repeated measures design will be used to assess the effects of the intervention on symptoms of fatigue, depression, and pain over the course of treatment. At the end of treatment, focus groups will be conducted with study participants to assess their responses to the intervention and their perceptions of the system's value to both themselves and future cancer patients. In addition, the feasibility of the project, defined as the proportion of patients recruited into the study and the proportion of patient adherence to instructed use of the system, will be analyzed. Specific aims of the project include: 1) Develop the patient-centered communication intervention; 2) Conduct usability testing to ensure the successful completion of the intervention; 3) Examine study feasibility and patient reactions to the intervention; and 4) Evaluate intervention effects on pain, depression, and fatigue symptoms over time.

▶ Title: *Iyengar Effects for Breast Cancer Survivors with Persistent Fatigue* NCCAM
P.I.: Julienne Bower, Ph.D.
Institute: University of California, Los Angeles
Grant No.: 1 U01 AT003682-01
Study Type: Clinical
Award: $231,749

There are currently over 2 million breast cancer survivors in the United States, many of whom experience persistent cancer-related symptoms. Fatigue is the most common and distressing symptom among women successfully treated for breast cancer and causes serious disruption in quality of life. Mind-body interventions such as yoga are popular among cancer patients and have shown beneficial effects on fatigue in other populations; however, yoga trials in cancer are scarce. Based on promising results from a small, single-arm pilot study, the proposed study will evaluate the feasibility, acceptability, and preliminary efficacy of an Iyengar yoga intervention for breast cancer survivors with persistent fatigue. In this randomized, controlled trial, 60 breast cancer survivors with persistent cancer-related fatigue will be randomly assigned to yoga or health education control for 12 weeks and followed for 3 months. The aims of the project are to: 1) determine the feasibility and acceptability of a 12-week Iyengar yoga intervention for breast cancer survivors with persistent fatigue as compared with health education control; 2) evaluate the effects of yoga vs. health education on fatigue and physical performance in breast cancer survivors with persistent fatigue; and 3) explore the effects of yoga vs. health education on behavioral and immune outcomes associated with cancer- related fatigue, including depressed mood, sleep, pain, proinflammatory cytokine activity, and quality of life. This project will constitute the first randomized, controlled trial of yoga for fatigue in breast cancer survivors and will provide key preliminary data to support a larger efficacy trial. In addition, the study will provide insight into secondary effects of yoga and generate hypotheses about potential mechanisms for intervention effects that can be systematically evaluated in a larger trial. The development of targeted treatments for cancer-related fatigue is critical for maintaining quality of life in the growing population of breast cancer survivors.

▶ Title: *Qigong Effects on Fatigue and Cognitive Function after Treatment Breast Cancer* NCCAM
P.I.: Linda Larkey, Ph.D.
Institution: University of Arizona
Grant No.: 1U01 AT002706-01
Study Type: Clinical
Award: $188,039

Patients with breast cancer often report deficits in quality of life (QOL), including fatigue and cognitive dysfunction, that persist after treatment ends. One of the CAM modalities that breast cancer patients choose is the Traditional Chinese Medicine (TCM) based practice of Qigong. The investigators propose to test potential effects of a set of Medical Qigong practices on QOL in survivors of Stage II or III breast cancer, age 40-65. Patients who are 2-12 months past treatment for breast cancer and meeting eligibility criteria for fatigue and cognitive dysfunction will be randomized to a 3-month intervention, either (a) a series of gentle Medical Qigong (MQ) exercises developed and supervised by a Doctor of Oriental Medicine/Master of Qigong and specifically designed for women recovering from breast cancer or (b) Restful Movement (RM), a series of stretches and movements based on the Lebed method of rehabilitation and lymphedema-preventative exercises for breast cancer patients, 30 participants in each group. The Restful Movement protocol will not be designed to emphasize movement of Qi (that is, will not include breath training nor teach about moving/allowing Qi flow that is central to Qigong practice). Primary endpoints will be assessed using (a) FACIT-F (fatigue and other QOL factos) and (b) objective measures of cognitive performance including Digit-Span and Letter/Number Sequencing tests of attention and working memory.

Specific Aim 1. To test whether Medical Qigong (MQ) practiced with conscious breathing techniques, visualization and intent to balance Qi is more effective than Restful Movement (RM) for improving QOL in women after treatment for breast cancer. Hypothesis One: MQ will improve levels of fatigue in breast cancer survivors more than RM. Hypothesis two: MQ will improve cognitive function in breast cancer survivors more than RM. Specific Aim 2.To examine (a) mechanisms possibly associated with purported effects of MQ and (b) alternate explanations for effects. Blood analyses for all participants will examine lymphocyte counts, T cell subsets, and serum cytokines. If findings are positive, results will be used to plan an RO1 proposal to test Medical Qigong against both RM and a usual care control, powered for significance, including more extensive tests for mechanisms of action potentially influencing outcomes related to Qigong practice on fatigue, cognitive function and immunity, and track disease progression outcomes.

▶ Title: *2006 NIH Director's Pioneer Award* OD and NIGMS
P.I.: Rosalind Segal, M.D., Ph.D.
Institution: Dana Farber Cancer Institute
Grant No.: 1 DP11 OD000839-01
Study Type: Basic
Award: $500,000

The PI is an associate professor of neurobiology at Harvard medical School and a member of the department of Pediatric oncology at the Dana Farber Cancer Institute. She is trained as a physician and a cell biologist, and her laboratory focuses on the biology of brain tumors by probing the complex molecular machinery of the developing brain. Her research aims to understand the mechanisms critical for normal development of the nervous system and how deregulated proliferation, migration, and survival of cells can cause brain tumors and other neurological diseases. Dr. Segal will use her Pioneer Award for genetic and biochemical studies to identify the way complex sugars work to maintain neural stem cells in the developing and adult brain.

Cardiovascular Disease

▶ Title: *Genetics of Early-Onset Stroke* NINDS
P.I.: Steven J. Kittner, M.D.
Institution: University of Maryland, School of Medicine, Baltimore
Grant No.: 5 R01 NS045012-04
Keywords: ischemic stroke, thrombomodulin, protein C, fibrinolysis systems, endothelial protein C receptor, plasminogen activator inhibitor-1, endothelial protein receptor polymorphisms, African-American, Caucasian, brain disorders, cardiovascular, genetics, prevention
Study Type: Clinical
Award: $292,950

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 popula-

tion-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 CVD* NHLBI

P.I.: Maureen J. Charron, Ph.D.
Institute: Albert Einstein College of Medicine, Bronx, NY
Grant No.: 5 R01 HL073163-04
Keywords: metabolic disturbances, cardiovascular disease, insulin-stimulated GLUT4 transporter, diabetes, genetics, obesity, prevention
Study Type: Basic
Award: $195,301

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 over-express 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.

▶ Title: *Inflammation and Insulin Resistance in Peripheral Arterial Disease* NHLBI
P.I.: Mark A. Creager, M.D.
Institution: Brigham and Women's Hospital, Boston
Grant No.: 3 R01 HL075771-04
Keywords: PAD, CVD, sex differences, inflammatory
Study Type: Epidemiologic (Case-Control)
Award: $10,000

Patients with peripheral arterial disease (PAD) frequently have functional limitations and symptoms of claudication that impact adversely on their quality of life. Many progress to critical limb ischemia requiring revascularization. Vascular inflammation and insulin resistance are two important and interdependent conditions that are associated with atherosclerosis. Moreover, both inflammation and insulin resistance cause abnormalities in vascular function and insulin resistance interferes with skeletal muscle metabolism. As such, inflammation and insulin resistance provide attractive targets for therapy that could potentially ameliorate the development of symptomatic PAD or improve the function and clinical outcomes of patients with PAD. Accordingly, the applicants propose three specific aims to determine whether inflammation and insulin resistance contribute to the functional and clinical consequences of PAD. First, a prospective, nested, case-control evaluation will be performed to test the hypothesis that baseline plasma levels of inflammatory cytokines (e.g. interleukin (IL)-4, IL-6, IL-18, macrophage inhibiting cytokine-1, CD 40 ligand) among healthy men are associated with the development of future symptomatic PAD. Second, to test the hypothesis that inflammation and insulin resistance contribute to reduced walking distance in patients with intermittent claudication by impairing vascular reactivity and skeletal muscle metabolic function, plasma markers of inflammation and insulin resistance, endothelium-dependent and independent vasodilation (by vascular ultrasonography) and skeletal muscle glucose utilization (by [18F] FDG positron emission tomography) will be measured before and after 12 weeks of treatment with rosiglitazone, atorvastatin or placebo in a 2x2 factorial design protocol. Third, to test the hypothesis that inflammation and insulin resistance are associated with the incidence and progression of vein graft disease in patients undergoing lower extremity vein bypass, functional and morphologic changes in vein grafts (measured by ultrasound and magnetic resonance imaging) will be assessed and related to inflammation and insulin resistance and to a composite clinical outcome of graft occlusion, reintervention or major amputation. It is anticipated that the findings from this investigation will uncover novel pathophysiologic mechanisms and foster a new paradigm for the treatment of PAD.

▶ Title: *Yoga and Incidence of Cardiovascular disease in Older Women* NCCAM
P.I.: Karen (Kim) Innes, Ph.D.
Institution: University of Virginia
Grant No.: 1R21 AT0029820-01A1
Study Type: Clinical
Award: $302,999

This research will investigate the effects of Iyengar yoga on insulin resistance syndrome (IRS) and related indices of cardiovascular disease (CVD) in postmenopausal women. CVD is the leading cause of death for U.S. women, and its risk rises sharply with the onset of menopause. It is observed that yoga may reduce IRS-related risk factors for CVD. This study is important to women's health because it involves menopause, which brings physiological changes during a woman's lifespan. Second, the intervention fits areas of research in both a preventive and therapeutic intervention for progressive disorders that affect women such as CVD and IRS. As an alternative modality, Iyengar yoga promotes wellness in older women and may prevent disease progression (e.g., osteoporosis) and may possibly alter disease initiation (e.g., CVD). In addition, the study is interdisciplinary and focuses on an area of importance to postmenopausal women - - the increased mortality of CVD.

Craniofacial

▶ Title: *Brief Focused Treatment for TMD: Mechanisms of Action* NIDCR
P.I.: Mark D. Litt, Ph.D.
Institution: University of Connecticut, School of Medicine, Farmington, CT
Grant No.: 5 R01 DE014607-04
Keywords: temporomandibular disorders (TMD), pain, coping, mood, cortisol, cytokines, behavioral and social science, dental/oral disease, chronic pain conditions
Study Type: Clinical
Award: $97,650

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 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 6 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 hand-held 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 follow-up points thereafter up to a 12-month follow-up. 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 TMJD Vulnerability Types* NIDCR
P.I.: Christian S. Stohler, D.M.D.
Institution: University of Maryland Professional School, Baltimore
Grant No.: 5 R01 DE015396-04
Keywords: temporomandibular, pathogenesis, candidate gene, estrogen, dental/oral disease, genetics, chronic pain conditions
Study Type: Basic and Clinical
Award: $97,650

Temporomandibular joint disorders 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 TMJ and Fibromyalgia* NIDCR

P.I.: Dean A. Dessem, Ph.D.
Institution: University of Maryland Dental School, Baltimore
Grant No.: 5 R01 DE015386-04
Keywords: temporomandibular, fibromyalgia, neurons, musculoskeletal, gender, dental/oral disease, chronic pain conditions
Study Type: Basic
Award: $97,650

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, 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, 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 a) spontaneous and evoked activity and b) 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 TMJ* NIDCR
P.I.: Phillip R. Kramer, Ph.D.
Institution: Texas A and M University Health Science Center, Dallas
Grant No.: 5 R01 DE015372-04
Keywords: gene, macrophage, rheumatoid factor, dental/oral disease, estrogen, TMJ disorders
Study Type: Basic
Award: $97,650

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 post-partum 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-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-alpha and IL-1 alpha will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim two 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-alpha and IL-1 alpha promoter sequences. Aim three will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ER alpha and/or ER beta will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

▶ Title: *Mast Cell Role in Masseter Muscle Repair* NIDCR
P.I.: Joyce A. Morris-Wiman, Ph.D.
Institution: University of Florida, Gainesville
Grant No.: 5 R21 DE016317-03
Keywords: TMJ, pain, inflammation, dental/oral disease
Study Type: Basic
Award: $97,650

Temporomandibular disorders (TMD) affect approximately 12% of the US population, predominately women in their childbearing years and of those affected by TMD, greater than 60% 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: *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
Grant No.: N01 DE22635
Keywords: TMJ, medical devices, chronic pain conditions, dental/oral disease
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: *A Systems Approach to the Understanding of TMJ as a Complex Disease* NIDCR
P.I.: Allen Cowley
Institution: TMJ Association, Brookfield, WI
Grant No.: 1 R13 DE017854-01
Keywords: meeting, temporomandibular joint syndrome
Award: $5,000

The Fourth Scientific Meeting of TMJ Association, A Systems Approach to the Understanding of TMJ as a Complex Disease,, was held in September, 2006 in Bethesda, Maryland. Based on a 1989 national survey conducted by the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH), an estimated 10 million people in the United States have signs of temporomandibular diseases and disorders, commonly referred to as "TMJDs," with as many as 90 percent of treated patients being women in their childbearing years. Since little research had explored these problems, in the years 2000, 2002, and 2004 The TMJ Association, a national patient advocacy organization, planned and organized scientific meetings (co- sponsored by agencies of the NIH) to assess the current state of the science and provide directions for future research. These highly successful meetings were held with the fundamental goal of enriching the pool of investigators directed to TMJ research by attracting experts from other fields and by stimulating the interest of young investigators in the emerging field. The summaries and future research recommendations of these meetings have been published. It is evident from these meetings that TMJDs fit the profile of a complex disease extending far beyond dysfunction and pain of the jaw joint. Therefore, the specific aims of the next proposed meeting are: 1. To convene expert clinical and basic scientists to characterize the multiple symptoms and co-morbid conditions found in TMJD patients (and exemplified by reports of patients attending the meeting) in order to develop research strategies based on an integrated and cross-disciplinary platform. The aim would be to combine resources from diverse fields to examine the etiology, diagnosis, pathogenesis, and treatment of patients with TMJDs from a new perspective, 2. To promote the participation of students and young clinical investigators through a Travel Award Program and encourage their involvement in discussions that reflect

the challenges of pursuing the interdisciplinary studies necessary to advance understanding of TMJDs as a complex disease, and 3. To develop a compelling set of recommendations for research initiatives in TMJDs that would synergize the work of multiple Institutes and Centers of the National Institutes of Health and that of academic health centers. Treatments for temporomandibular joint diseases and disorders (TMJDs) currently leave much to be desired and it is imperative that the underlying biology that drives these conditions be reexamined at this time. This meeting will look at TMJDs as a complex disease involving genetic factors, environmental conditions, as well as risk and confirmed behaviors mediating the vulnerability of patients to TMJDs.

Diabetes

▶ Title: *Diabetes Prevention Program Outcomes Study (DPPOS)* NIDDK
P.I.: Sarah Fowler, Ph.D.
Institution: George Washington University, Washington, DC
Grant No.: 5 U01 DK048489-13
Keywords: diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention, cardiovascular disease
Study Type: Clinical
Award: $292,950

The Diabetes Prevention Program (DPP) addressed its primary objective, establishing the efficacy of lifestyle modification and metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for an average of 2.8 years; however, many important issues remain unanswered. Specifically, whether the decrease in the development of diabetes can be sustained is unknown. Moreover, determining whether the delay or prevention of diabetes will translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease, all of which require more years to develop than the DPP period of study, is critical to establish the true impact of the DPP on public health. The long-term follow-up study of the DPP, entitled the Diabetes Prevention Program Outcomes Study or DPPOS, is designed to evaluate the long-term effects of active DPP interventions on the development of a) diabetes during a further 5-11 years of follow-up and b) composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both the continued lifestyle intervention and metformin will provide continued separation in the rates of diabetes development, compared with the former placebo group, and that the prevention or delay of diabetes during the DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status. The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

Gastroenterology

▶ Title: *Improving IBS Outcomes* NINR
P.I.: Margaret M. Heitkemper, Ph.D.
Institution: University of Washington, Seattle
Grant No.: 5 R01 NR04142-09
Keywords: irritable bowel syndrome (IBS), polymorphisms, gender, serotonin, behavioral and social science, digestive disease, chronic pain conditions
Study Type: Translational
Award: $97,650

In the United States, it is estimated that 10-20% 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.: 5 U01 DK070234-03
Keywords: urinary frequency, bladder pain, patient screening, survey research, quality of life, endometriosis, interstitial cystitis, chronic pain conditions, urologic disease
Study Type: Epidemiological
Award: $195,300

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; (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: *Epigenetics X-linked Genes In PBS: Does X Mark the Spot?* NIDDK
P.I.: Carlo Selmi, Ph.D.
Institution: University of California, Davis
Grant No.: 1 R21 DK075400-01
Study Type: Clinical
Award: $189,479

Primary Biliary Cirrhosis (PBC) is an autoimmune chronic cholestatic liver disease with a striking female predominance (90% symptomatic cases are females age 35-60). Women with PBC have a significantly enhanced monosomy X frequency in peripheral white blood cells compared to age- and disease stage-matched women with chronic viral hepatitis and to age matched healthy women. The random X chromosome inactivation (XCI) in women is caused by epigenetic mechanisms such as DNA methylation. However, there are 125 X-linked genes that exhibit widely variable patterns of inactivation between individuals. The investigators hypothesize that susceptibility to PBC arises from individual epigenetic modifications of specific genes on the X chromosome, either with protective genes being silenced or susceptibility genes escaping inactivation. This research brings together evidence on enhanced monosomy X in autoimmunity and variable X chromosome inactivation patterns, and also takes advantage of a unique series of MZ twins and siblings concordant and discordant for PBC to focus on a question that is likely to have implications for other autoimmune disorders as well. This project will expand our understanding of sex differences that may modify the role of known cellular pathways and gene defects in disease.

HIV/AIDS

▶ Title: *Microbicides Innovation Program (MIP)* OAR, NIAID, NICHD, NIMH
Study Type: Fourteen basic science grants funded through the MIP program
Award: $200,000

ORWH is partnering with the Office of AIDS Research, NIAID, NICHD and NIMH to support an innovative R & D program to advance new microbicides. A total of fourteen (14) grants were funded in FY 2006, through NIAID, NICHD or NIMH. This research is important because the most dominant means of transmission of HIV and spread of AIDS worldwide is by heterosexual intercourse. Microbicides, compounds that could be used in vaginal and rectal formulations, are increasingly seen as an urgent goal to stop transmission. The ability of a combination of antiviral agents to effectively prevent HIV transmission will be evaluated in newly developed and well established in vitro assays specifically designed to enhance the characterization and discovery of effective combination microbicide therapies. This innovation program will serve to develop an appropriately formulated and acceptable products, with a highly defined biological profile including efficacy, toxicity, biopolymer properties and effectiveness as a biological barrier to HIV transmission. It is anticipated that the proposed research will yield significant advancements

in microbicide biology and chemotherapy in several different areas, including the development of new and novel microbicide agents, the definition and validation of combination therapeutic strategies for microbicide use, the development of new in vitro tools for evaluating the clinical potential of microbicides, and the development of novel formulations designed to complement both the antiviral capacity of the combination therapy and the social issues of acceptability.

▶ Title: *Impact of Delivery Models in HIV Health Care* FIC
P.I.: Ximena L. Burbano, M.D.
Institution: Fundacion Santa Fe de Bogota, Bogota, Colombia
Grant No.: 5 R01 TW006218-04
Keywords: HIV/AIDS, health services research, prevention, infectious diseases
Study Type: Clinical
Award: $19,530

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
Grant No.: 5 R01 TW006640-04
Keywords: HIV/AIDS, postpartum, counseling, prevention, topical microbicides
Study Type: Clinical
Award: $19,530

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-1transmission, 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 trans-

mission 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 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; 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 (AITRP)* FIC
P.I.: Arthur L. Reingold, M.D.
Institution: University of California, School of Public Health, Berkeley
Grant No.: 3 D43 TW000003-07
Keywords: training, virology, HIV/AIDS, infectious diseases
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 International AIDS Training 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 on-going 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 proposal 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; 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: Weill Medical College of Cornell University, New York, NY
Grant No.: 3 D43 TW000018-19
Keywords: infectious diseases, epidemiology, biosocial, HIV/AIDS, treatment and prevention, rural health
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., PhD, 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% 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 (AITRP)* FIC
P.I.: King K. Holmes, M.D., Ph.D.
Institution: University of Washington, College of Medicine, Seattle
Grant No.: 5 D43 TW000007-19
Keywords: HIV/AIDS, international, prevention, treatment, immunology, infectious diseases, vaccine development
Study Type: Clinical
Award: $50,000

This program proposes to develop a fifth International AIDS Research and Training Program (IARTP) 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) IARTP 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 Infec-

tious Diseases (ITREID) has a site in New Delhi and the two programs will collaborate in their research and training efforts in the region. The IARTP 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: a) Strengthening of the infrastructure for field research through training and capacity building in the area, b) Development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, c) 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-term 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: a) Seroprevalence and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, b) Clinical profile of HIV-1 clade C infection in India, c) Cellular immunity to HIV-1clade C viruses and diversity consideration in vaccine development, and d) 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: *Mentor Mothers: A Sustainable Family Intervention in S. African Townships* NIMH
P.I.: Mary Rotherham-Borus, Ph.D.
Institution: University of California, Los Angeles
Grant No.: 1 R01 MH077553-01
Study Type: Clinical
Award: $300,000

The number of women living with HIV continues to rise globally, and it has reached crisis levels in South Africa. In specific provinces such as KwaZulu-Natal, the rate of HIV infection among pregnant women was 40.7% in 2004, an increase from 36.5% in 2002 (Department of Public Health, South Africa, 2004). This project focuses on quality of life for these women by evaluating an intervention designed to improve the lives of HIV-positive women and their babies in South Africa. The research builds on an existing social service program that is operating in KwaZulu-Natal (The Mothers' Programmes - TMP) and transforms it into a theoretically based, sustainable behavioral prevention program (Mothers-To-Mothers - M2M). TMP has garnered a great deal of interest on the part of policy makers. While TMP has been perceived as being highly successful, there are no data supporting the related outcomes. Given the dramatic scale of the Mother to Child Transmission (MTCT) programs in southern Africa, information from this study will provide guidelines for psychosocial interventions with pregnant women living with HIV on how to parent effectively and prevent the transmission of the virus to their child while coping effectively with this chronic illness.

Immunity/Autoimmunity

▶ Title: *Sex-Based Differences in the Immune Response* NIAID
P.I.: Betty Diamond, M.D.
Institution: Albert Einstein College of Medicine, New York, NY
Grant No.: 5 R01 AI51767-05
Keywords: autoimmunity, hormones, animal models, estrogen
Study Type: Basic
Award: $48,825

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 3 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: *Predictors of Pregnancy Outcome in SLE and APS* NIAMS
P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 5 R01 AR049772-04
Keywords: thrombosis, pregnancy loss, systemic lupus erythematosus, antiphospholipid antibodies, genetic polymorphisms, recurrent fetal loss, poor fetal outcome, placentas, autoimmune diseases, genetics, prevention
Study Type: Clinical
Award: $390,600

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 obser-

vational study of over 400 pregnant patients, enrolled at 6 major clinical centers, and grouped and analyzed according to the presence or absence of aPL and preexisting 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: Johns Hopkins University, Baltimore, MD
Grant No.: 5 R01 AR49125-05
Keywords: systemic lupus erythematosus, cognitive dysfunction, basic behavioral, behavioral and social science, brain disorders, depression, fibromyalgia, mental health
Study Type: Clinical
Award: $97,650

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 10 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: *Antibodies to NR2 in SLE* NIAMS
P.I.: Betty Diamond, M.D.
Institution: Yeshiva University, New York, NY
Grant No.: 5 R01 AR49126-05
Keywords: NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, human tissue, brain disorders
Study Type: Clinical
Award: $78,120

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: *EBNA-1 in Lupus* NIAID
P.I.: John B. Harley, M.D.
Institution: Oklahoma Medical Research Foundation, Oklahoma City
Grant No.: 5 R01 AI31584-13
Keywords: systemic lupus erythematosus, Epstein-Barr virus, Epstein Barr virus, B lymphocyte, autoimmune disorder, cytomegalovirus
Study Type: Basic
Award: $195,300

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-lmmediate 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 expres-

sion, 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: *UCSF Autoimmunity Center of Excellence (ACE)* NIAID
P.I.: David Wofsy, M.D.
Institution: University of California, San Francisco
Grant No.: 5 U19 AI056388-04
Keywords: immunology, molecular biology, autoimmune diseases, clinical trials, immunotherapies, murine lupus, lupus nephritis, diabetes, multiple sclerosis, prevention, urologic disease
Study Type: Clinical
Award: $58,600

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 as described below: 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 costimulation 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 Costimulatory Signal (ACE)* NIAID
P.I.: Samia J. Khoury, M.D.
Institution: Brigham and Women's Hospital, Boston
Grant No.: 5 U19 AI046130-08
Keywords: autoimmune disease, prevention, autoimmune disorder, immunotherapy, clinical research
Study Type: Clinical
Award: $58,600

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 costimulatory 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 (ACE)* NIAID

P.I.: Ignacio Sanz, M.D.
Institution: University of Rochester, NY
Grant No.: 5 U19 AI056390-04
Keywords: diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, autoimmune diseases, pathogenesis, disease-specific autoantibodies
Study Type: Clinical
Award: $58,600

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 reagents 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 (ACE)* NIAID
P.I.: Eugene W. St. Clair, M.D.
Institution: Duke University, Durham, NC
Grant No.: 5 U19 AI056363-04
Keywords: B cell responses, immunotherapy, autoimmune diseases, lupus, arthritis
Study Type: Clinical
Award: $58,600

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: *UAB Autoimmunity Center for Excellence (ACE)* NIAID
P.I.: Robert H. Carter, M.D.
Institution: University of Alabama at Birmingham
Grant No.: 5 U19 AI056542-04
Keywords: translational therapies, immunology, autoimmune diseases, autoimmune disorder, autoimmunity, cooperative study, clinical research
Study Type: Clinical
Award: $58,600

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: *Immunoregulatory Effects of Estrogen in EAE* NINDS
PI: Halina Offner, Ph.D.
Institution: Oregon Health and Science University
Grant No: 1 R01 NS045445-01
Study Type: Basic
Award: $250,000

Multiple sclerosis (MS) is but one human autoimmune condition with a strong overrepresentation in women. Sex hormones are considered prime suspects for this gender dimorphism. Symptoms of MS improve during pregnancy with increased levels of sex hormones and worsen post-partum, when these levels fall. This gender susceptibility is also seen in EAE, an animal model for MS, where estriol and synthetic estrogens were shown to suppress disease. This research aims to determine the cell types responsible for this estrogen receptor-mediated protection and to evaluate the role of PD-1 and its ligand. PD-1, a member of the immunoglobulin superfamily, plays a crucial role in peripheral tolerance. The last aim investigates the therapeutic and neuroprotective effects of estrogens in a series of EAE models. This aim is of utmost importance as clinical trials of estriol therapy in female MS patients are being developed and will be influenced by finding s form this research.

▶ Title: *International Research Registry Network for Sjögren's Syndrome* NIDCR
P.I.: John S. Greenspan, Ph.D.
Troy Daniels, D.D.S., M.S.
Institution: University of California, San Francisco
Grant No.: N01 DE32636
Keywords: research registry, Sjogren's syndrome, international, dental/oral disease
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; and 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.

Infectious Diseases

▶ Title: *Seroprevalence/Incidence of Genital Herpes* FIC
P.I.: Edith Nakku-Joloba, Ph.D.
Institution: New Mulago Hospital, Kampala, Uganda
Grant No.: 5 R01 TW006672-04
Keywords: herpes, epidemiology, infectious diseases, prevention, rural health, vaccine related
Study Type: Public Health, Clinical
Award: $19,530

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 i) To estimate the age and sex specific prevalence of Herpes simplex type 1 and 2. ii). To estimate the incidence of Herpes simplex type 1 and 2 in an inception cohort of HSV-2 negative persons in an urban population in Uganda and iii) to identify modifiable risk factors associated with Herpes simplex types 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 herpes simplex type 1 and 2. Incidence will be assessed in an inception cohort of HSV-2 negative persons by 6 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: *The Study of Women's Health Across the Nation (SWAN III)* NIA
P.I.: Kim Sutton-Tyrrell, Ph.D.
Institution: University of Pittsburgh
Grant No.: 5 U01 AG012553-12
Keywords: aging, hormones, menopause, minorities, reproductive aging, risk factors, CAM, diabetes, hypertension, kidney-incontinence, behavioral and social science, cardiovascular
Study Type: Clinical
Award: $244,125

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%) 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 (two 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 follow-up. 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, Los Angeles
Grant No.: 5 U01 AT001653-04
Keywords: hormone therapy, soy protein, isoflavone-rich, soy protein, postmenopausal women, atherosclerosis, common carotid artery, estrogen, cancer, cardiovascular, CAM
Study Type: Clinical
Award: $195,300

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 1 killer of postmenopausal women.

▶ Title: *Biology of the Perimenopause: Impact on Health and Aging in Non-Reproductive Somatic and Neuronal Tissue* NIA
Study Type: Basic, Clinical
Award: $450,000

Partnering with NIA, ORWH co-funded nine (9) new grants in this area. The goal of this RFA was 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. The NIH was most interested in studies relating to how the hypothalamic-pituitary-ovarian axis hormone levels and dynamic changes in hormone levels across the menopausal transition affect pathophysiologic processes within non-reproductive somatic and neuronal target tissues. Other scientific areas of interest included the role of steroid hormone biosynthesis and/or metabolism within non-reproductive somatic and neuronal tissues on pathophysiologic processes within these tissues across the perimenopause, and the role of aging on these pathophysiologic processes. Research projects from this RFA included studies looking at women across the menopausal transition or biospecimens from that group of women. These studies will focus on the roles of estrogen and glucocorticoids in abdominal adiposity, skeletal and vascular health; the effects of cytokine secretion under FSH regulation; the role of estrogen and age in arterial stiffening; and the patterns of brain activation during cognitive and emotional tasks. A second group of studies will utilize an animal model (female rodents) undergoing reproductive aging. These studies will focus on how reproductive aging and estrogen modulate the inflammatory environment of the brain and periphery, the estrogen sensitive neuronal systems of the hypothalamus and effects on prolactin secretion, the survival and function of hippocampal neurons in collaboration with IGF-I in a global ischemia model, and the transcriptional activation of estrogen receptors by non-estrogenic activators as well as estrogen.

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.: 5 R01 MH65871-05
Keywords: mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/alcohol abuse, clinical research, human subjects, behavioral and social science
Study Type: Clinical
Award: $170,887

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 U.S. With these interview data, we will test a theoretical model of

stress and coping specific to this population. Sub-aims are to (a) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); (b) test the direct associations between trauma and health outcomes; (c) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and (d) 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: *Youth Suicide Prevention Using Community-Based, Participatory Research Methods to Design and Implement the Apache Youth Suicide Research and Prevention Program* — IHS

P.I.: Maridde J. Craig; John Walkup, M.D.
Institution: White Mountain Apache Tribe, Whiteriver, AZ; Johns Hopkins University School of Medicine, Baltimore, MD
Grant No.: 5 S06 GM074004-02
Keywords: adolescent, Native American, mental health, prevention, suicide
Study Type: Clinical
Award: $75,000

The White Mountain Apache Tribe and Johns Hopkins Center for American Indian Health Native American Research Center in Health proposes to employ community-based, participatory research methods to design and implement the Apache Youth Suicide Research and Prevention Program for the White Mountain Apache Tribe in Whiteriver, Arizona. Rates of suicide among youth and young adults on the White Mountain Apache Reservation have been among the highest in the U.S. of any ethnic group in the past decade. The White Mountain Apache and Johns Hopkins have collaborated for more than 25 years in addressing the health and social priorities of the Tribe, with findings from past work generalized across Indian country and the world. To develop the Apache Youth Suicide Research and Prevention Program we will: (1) develop a surveillance and data collection system for the evaluation of suicidal behavior on the White Mountain Apache Reservation; (2) collect and analyze data from young suicide attempters (<19 years old) to identify key characteristics and determinants of suicidal behavior in this age group; (3) engage community experts in the development of a suicide prevention program that utilizes empirically supported prevention intervention strategies to target key determinants and characteristics in at risk Apache youth; and (4) develop a NIH grant proposal to test the efficacy of the Youth Suicide Prevention Program developed during the period of this award. The outcomes of this work will provide important models for other communities battling this increasing problem among adolescents and young adults.

▶ Title: *Antimanic Use during Pregnancy* — NIMH

P.I.: Katherine Wisner, M.D.
Institution: University of Pittsburgh
Grant No.: 1 R01 MH075921-01
Study Type: Clinical
Award: $200,000

Bipolar disorder (BP) is a serious psychiatric condition that affects 0.5 -1.5% of individuals in America. The age of onset of BP is during the initial childbearing years. Seventy percent of women with established

BP will suffer recurrent episodes post-birth. Continuous medication administration is the mainstay of treatment for BP. Although the information available to physicians who treat pregnant women with unipolar depression has increased over the past decade, data to inform decisions about treatment of BP has not advanced similarly. Information about anticonvulsant use during pregnancy has been garnered solely from the study of women with epilepsy, who have increased risk for malformations independent of drug treatment. Data about atypical antipsychotic use in pregnancy is almost non-existent in either women with BP or schizophrenia. The majority of studies have not included the range of outcome measures that comprise the contemporary portfolio of the reproductive toxicity outcomes. Pharmacologists have produced data for altered physiologic states (renal or hepatic disease) and for other patient subpopulations (children and elderly). The need for similar studies in pregnancy is certainly no less than for these populations. New information must be obtained to guide risk-benefit decision-making to a new level of sophistication. This is a prospective observational study of women with BP during pregnancy and the mother-infant pairs n the first postpartum year. The researchers plan to enroll 200 women with BP and 58 women without BP (for 140 and 40 completers, respectively). Decisions about treatment during pregnancy will be made by the woman with her physician (not associated with the study) prior to study enrollment. The major aims of the study are to define a cohort of pregnant women with DSM-IV defined BP and to: 1) Characterize the BP illness course in the population through pregnancy and the first postpartum year, with careful documentation of treatment(s) and gestational timing. 2) Evaluate function in the maternal role as well as occupational, educational and social domains. 3) Define pregnancy and infant outcomes in both medicated and unmedicated women with BP and compare them to those of unmedicated women without BP. Separation of the effects of medication from the disorder is critical to advance risk assessment. 4) Assess the infants' development through the first year of life. 5) Perform serum levels at 20, 30, and 36 weeks gestation to allow level/dose ratio monitoring for women who take medications during childbearing. The mother-infant serum levels of women with BP who breastfeed their infants also will be assayed. 6) Conduct pharmacokinetic (PK) studies on the subset of women who take lithium, the most common drug used to manage BP during pregnancy in our Center, at 20- 24 weeks, 32-36 weeks, and 12-16 weeks after birth. No such PK data are currently available.

Musculoskeletal Systems

▶ Title: *Osteo-Arthritis Initiative (OAI)—Baltimore* NIAMS

P.I.: Marc Hochberg, M.D.
Institution: University of Maryland School of Medicine, Baltimore
Grant No.: N01-AR-2259
Keywords: biological markers, osteoarthritis, disease progression
Study Types: Clinical
Award: $67,033

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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: *Osteo-Arthritis Initiative (OAI) -- Columbus* NIAMS
P.I.: Rebecca Jackson, M.D.
Institution: Ohio State University, Columbus
Grant No.: N01-AR-2261
Keywords: biological markers, osteoarthritis, disease progression
Study Type: Clinical
Award: $524,739

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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: *Osteo-Arthritis Initiative (OAI) -- Pittsburgh* NIAMS
P.I.: C. Kent Kwoh, M.D.
Institution: University of Pittsburgh
Keywords: biological markers, osteoarthritis, disease progression
Grant No.: N01-AR-2260
Study Type: Clinical
Award: $208,228

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (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: GlaxoSmith-Kline, 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: *Bone-Sparing Effects of Soy Phytoestrogens in Menopause* NIAMS
P.I.: Silvina Levis, M.D.
Institution: University of Miami School of Medicine, Miami, FL
Grant No.: 5 R01 AR048932-04
Keywords: osteoporosis, menopause, hormone replacement therapy (HRT), prevention, estrogen
Study Type: Clinical
Award: $97,650

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years are 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.

▶ Title: *Impaired Acyl-CoA Synthetase-Muscle Lipid Oxidation in African-American Women* NIDDK
P.I.: Ronald Cortright, Ph.D.
Institution: East Carolina University
Grant No.: R01 DK075880-01
Study Type: Clinical
Award: $263,625

This project will investigate cellular and molecular mechanisms that predispose African American Women (AAW) to develop obesity and Type 2 diabetes. Specifically, the reduction of skeletal muscle fatty acid oxidation in obese and normal AAW compared to Caucasian women will be investigated. This reduction may provide a mechanistic link for increases in the development of insulin resistance, obesity and diabetes in AAW. The cellular site and specific isoform(s) of reduced Acyl-CoA synthase activity will be identified in isolated human muscle strips using the latest molecular siRNA and adenovirus transfection technologies through an interdisciplinary collaboration of investigators. Possible differences in exercise training induced changes that may ameliorate the inherent fatty acid oxidation differences will also be explored with the potential of developing new therapeutic strategies for treatment of obesity and diabetes in AAW.

Nutrition

▶ Title: *Botanical Supplements for Women's Health* NCCAM
P.I.: Norman R. Farnsworth, Ph.D.
Institution: University of Illinois at Chicago
Grant No.: 5 P50 AT000155-07
Keywords: menopause, botanicals, dietary supplements, CAM, estrogenic effects
Study Type: Basic, Clinical
Award: $97,650

Since the 1994 DSHEA mandate, botanical dietary supplements (BDSs) are continuously developing into safer and more effective preparations that aid U.S. public health. Since its establishment in 1999, our BOTANICAL CENTER has participated in this development by performing significant (bio-)chemical and clinical research on BDSs that are widely used to restore and/or maintain women's health. The focus of a renewed grant period will continue to be the alleviation of perimenopausal and premenstrual syndrome (PMS) symptoms. Linked to this focus is the central hypothesis that botanicals contain potent secondary plant metabolites that exhibit activities in estrogenic and major CNS (serotonin, GABA, dopamine, and opioid) systems. In close collaboration with the other projects of the CENTER, PROJECT 1 will (Aim 1) evaluate and prioritize select botanicals; (Aim 2) show that they contain phytoconstituents with the desired biological activities and profiles, in vitro and in vivo; isolate and structurally characterize these active principles by modern spectroscopical methods and use them to (Aim 3) standardize the botanicals. The long-term objective of this proposal is to prepare botanical extracts that are chemically and biologically standardized in terms of the bioactive secondary plant metabolite(s), and that are stable for human studies. Combining promising botanicals from the previous grant period with the results of preliminary studies, an initial selection of 12 plants plus two complex herbal mixtures will be evaluated. Primary extracts of a wide polarity range and their solvent partition fractions will be assayed in vitro and in vivo by PROJECTS 2+3, and prioritized using a scoring system that weighs hit numbers, grouping of potency, as well as strengths and concentration of activity. The botanicals with the highest rank will be scaled-up and subjected to an innovative bioassay-guided fractionation procedure (w/PROJECTS 2+3 and CORE B). The major active principles will be obtained through a sequential application of modern chromatography tailored to the specific characteristics of the extracts (HSCCC, Gel/Resin-CC). Modern qualitative and quantitative spectroscopic analysis (1/2D and selective NMR, qNMR, hyphenated MS) will lead to the identification of structures of the major active principles, which ultimately lays the foundation for chemical and biological standardization. Prioritized botanicals will be fully developed into standardized products. Hops will be evaluated in a Phase I clinical study in PROJECT 4.

▶ Title: *Bench to Bedside Research Program* Clinical Center and NIDDK
P.I.: Mark Levine, M.D. (Intramural)
Maret Traber, M.D. (Extramural)
Award: $80,750

ORWH is partnering with the NIH Clinical Center and NIDDK to co-fund two projects - -one based in the Intramural laboratories at the NIH Clinical Center, and the other with an extramural investigator, entitled Alpha-Tocoperol Modulation of Xenobiotic Metabolism.

Obesity/Overweight

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise* NIDDK
Weight Reduction for Incontinence Network (WIN)
P.I.: Deborah G. Grady, M.D.
Institution: University of California, San Francisco
Grant No.: 5 U01 DK860-04
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $97,650

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 and over 65% 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.

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise* NIDDK
Weight Reduction for Incontinence Network (WIN)
P.I.: Rena R. Wing, Ph.D.
Institution: Miriam Hospital, Providence, RI
Grant No.: 5 U01 DK67861-04
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $70,750

The specific aims of this study, are to determine whether randomization to a behavioral weight control program results in greater reductions in frequency of incontinence episodes at 6 months compared to usual care and to identify women who are most likely to experience improved incontinence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed), have not changed or been modified since funding. The study protocol and interventions have been designed to support the aims of this study. The study design is a multicenter randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month intensive behavioral weight reduction program or usual care (no weight reduction intervention) and followed for 18 months. After completing the intensive weight reduction program, a second randomization will be done to test whether an enhanced weight maintenance program results in superior long-term weight loss through 18 months compared to a standard maintenance program. In a subgroup of 100 women, we will perform standard urodynamic studies to allow us to evaluate the mechanism by which weight loss improves incontinence.

▶ Title: *PRIDE: Program to Reduce Incontinence by Diet and Exercise Weight Reduction for Incontinence Network (WIN)* NIDDK
P.I.: Frank Franklin, M.D., Ph.D.
Institution: University of Alabama, Birmingham
Grant No.: 5 U01 DK067862-04
Keywords: urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral and social science
Study Type: Clinical
Award: $70,750

The specific aims of this study, are to determine whether randomization to a behavioral weight control program results in greater reductions in frequency of incontinence episodes at 6 months compared to usual care and to identify women who are most likely to experience improved incontinence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed), have not changed or been modified since funding. The study protocol and interventions have been designed to support the aims of this study. The study design is a multicenter randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month intensive behavioral weight reduction program or usual care (no weight reduction intervention) and followed for 18 months. After completing the intensive weight reduction program, a second randomization will be done to test whether an enhanced weight maintenance program results in superior long-term weight loss through 18 months compared to a standard maintenance program. In a subgroup of 100 women, we will perform standard urodynamic studies to allow us to evaluate the mechanism by which weight loss improves incontinence.

▶ Title: *Health Outcomes of Weight-Loss: Data Coordinating Center (SHOW/Look AHEAD)* NIDDK
P.I.: Mark A. Espeland, Ph.D.
Institution: Wake Forest University, Winston-Salem, NC
Grant No.: 5 U01 DK57136-08
Keywords: obesity, health disparities, type 2 diabetes, clinical trials, sex differences, weight loss, physical activity, CVD risk factors, behavioral interventions, health promotion, disease prevention
Study Type: Randomized Clinical Trial
Award: $97,650

This application describes plans by an experienced group of investigators and staff at the Wake Forest University School of Medicine (WFU) to serve as the Coordinating Center (CoC) for the Study of Health Outcomes of Weight-Loss (SHOW). SHOW is a multicenter randomized trial designed to test whether weight loss interventions can reduce the progression of carotid atherosclerosis and other health outcomes in a cohort of 6000 obese type 2 diabetics. Participants will be randomized to one of 3 intervention arms: intensive lifestyle intervention (diet and exercise), intensive lifestyle intervention plus pharmacotherapy, or community control. The primary outcome is carotid intimamedial thickness. Secondary outcomes include cardiovascular (CV) and cerebrovascular events and death, CV risk factors, and glycemic control. Participants will be recruited over a 3-year period with 4-7 years of intervention and follow-up. WFU plans to operate the CoC for the SHOW trial. In that role, we will provide expert statistical support for sample size, data analyses and interpretation; collaborate in the design of SHOW and provide all supporting study documents including manuals and data collection forms; design and implement a web-based data management system; plan and support recruitment efforts in the 15 clinics; develop and monitor all quality control efforts; monitor recruitment, retention, the implementation of

the intervention, and adherence; subcontract with all Core Facilities (e.g., central laboratory); train and certify staff, perform study administrative duties; and participate in paper writing.

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.: 5 U10 EY13626-05
Keywords: blindness, quality of life, aging, Caucasian women, diabetes, eye disease and disorders of vision, macular degeneration
Study Type: Epidemiologic (Case-Control)
Award: $224,595

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

▶ Title: *Estrogen Receptors and Maintenance of Lens Transparency* NEI
P.I.: Vicki L. Davis, Ph.D.
Institution: Cedars-Sinai Medical Center, Los Angeles
Grant No.: 5 R01 EY014600-04
Keywords: ophthalmic diseases, aging, estrogen, cataract, estrogen receptor, lens, receptor expression, eye disorder chemotherapy, eye pharmacology
Study Type: Basic
Award: $132,549

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 2 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? 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 2 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 or 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: *Hormonal Cycles in Women: Effects on TMD Pain and Symptoms* NIDCR
P.I.: Linda Leresche, Sc.D.
Institution: University of Washington
Grant No.: 5 R01 DE016212-03
Keywords: TMJ, pain control, estrogen, depression, mental health, mind and body
Study Type: Translational
Award: $146,475

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: *Trigeminal Pain Mechanisms and Control: Mechanisms of Pain Caused by Disruption of Microtubules* — NIDCR

P.I.: Jon D. Levine, Ph.D.
Institution: University of California, San Francisco
Grant No.: 5 P01 DE08973-16
Keywords: pain control mechanism, orofacial neuropathies, neurosciences research, dental/oral disease, neurodegenerative
Study Type: Basic
Award: $168,176

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

▶ Title: *fMRI Measures of Central Sensitization in Migraine* — NINDS

P.I.: David Borsook, Ph.D.
Institution: McLean Hospital
Grant No.: 1 R01 NS056195-01
Study Type: Clinical
Award: $255,564

Migraine headache is one of the most common and debilitating chronic pain disorders, but the mechanisms underlying its etiology, pathophysiology, and progression have yet to be elucidated. With 18-20% of women affected by migraine, they are far more susceptible than men (3:1) and may experience migraines throughout their lifespan. Recent evidence shows migraine is a progressive disorder that can increase in frequency and cause structural damage to the nervous system. This finding highlights the need

to understand its pathophysiolgy. The PI is a highly respected investigator in the field and has developed a unique and innovative approach using fMRI to image the trigeminal nervous system during the course of a headache attack. His hypothesis targets the neurons whose enhanced activity is associated with migraine pain. The studies will elucidate the neuronal circuitry underlying the abnormal increases in pain sensitivity that headache sufferers experience during and between frequent headaches. Findings will help to identify subgroups of migraineurs who are likely to respond uniquely to different therapies, enabling tailored treatments to improve the quality of life for women throughout their lifespan. The studies enroll the collaboration of a physicist focused on imaging techniques, and with the PI, are leading experts in allodynia, or abnormal pain sensitivity, associated with migraine. This research focuses on a condition that primarily affects women and their quality of life.

▶ Title: *Redefining Diagnostic Criteria of a Pain Disorder: Vulvar Vestibulitis Syndrome* NICHD
P.I.: Dennis Zolnoun, M.D.
Institution: University of North Carolina
Grant No.: 1 K23 HD053631-01
Study Type: Clinical
Award: $139,572

Vulvar vestibulitis syndrome (VVS), the most common type of chronic vulvovaginal pain, impairs the psychological, physical, and reproductive health of nearly 1 in 10 women at some point in their lifetime. The etiology of VVS is poorly understood. The PI is a well-trained clinician who completed a Clinical Fellowship in Advanced Laparoscopy and Pelvic Pain, and has a master's in epidemiology. Her long-term career goal is to study the pathogenesis of VVS and how different pathophysiologic mechanisms influence heterogeneity among various subgroups of women with this disorder. The investigator will continue describing the disorder of VVS, and identify the underlying pathophysiological mechanisms that produce this condition.

Physical Activity

▶ Title: *Social Cognitive Theory and Physical Activity after Endometrial Cancer Intervention* NCI
P.I.: Karen M. Basen-Engquist, Ph.D.
Institution: University of Texas MD Anderson Cancer Center
Grant No.: 5 R01 CA109919-03
Keywords: physical activity, endometrial cancer, social cognitive theory
Study Type: Clinical
Award: $97,650

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 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 six-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every two 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.: Barry M. Popkin, Ph.D.
Institution: University of North Carolina, Chapel Hill
Grant No.: 5 R01 CA109831-03
Keywords: physical activity, physical environment, cardiovascular disease, race/ethnic differentials, coronary heart disease, prevention
Study Type: Clinical
Award: $97,650

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 18-30 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 life-cycle. 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.: Angela Bryan, Ph.D.
Institution: University of Colorado, Boulder
Grant No.: 5 R01 CA109858-03
Keywords: exercise behavior, cancer, cardiovascular disease, type II diabetes mellitus, physical activity, race/ethnicity, behavioral and social science, nutrition, prevention
Study Type: Clinical
Award: $97,650

Rates of cancer and cardiovascular disease have shown very little improvement over the past two decades, and the incidence of Type II diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30% 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% of the U.S. population do not get the recommended amount of physical activity as defined by 30 minutes of moderate intensity physical activity 5 or more days per week, and 40% 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) That 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: *Angiogenesis and Mechanisms of Exercise Training* NHLBI
P.I.: Brian H. Annex, M.D.
Institution: Duke University Medical Center, Durham, NC
Grant No.: 5 R01 HL075752-04
Keywords: artery, atherosclerosis, exercise, behavioral and social science, cardiovascular, chronic pain conditions
Study Type: Clinical
Award: $244,125

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5% of the US 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 exer-

cise 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: *ORWH-NICHD Leiomyoma Tissue Bank* NICHD
P.I.: James Segars, M.D.
Institute: NICHD, Bethesda, MD
Grant No.: 1 Z01 HD008737-06
Keywords: minority health, African American women, etiology, uterine fibroids (leiomyoma), reproductive health, benign tumors, gynecology
Award: $145,000

Health of 30-50% of women in the U.S. is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

▶ Title: *Protein Tyrosine Kinases in Leiomyomata Uteri* NICHD
P.I.: Jean Wang, Ph.D.
Institute: University of California, San Diego
Grant No.: 5 R01 HD046225-04
Keywords: protein tyrosine kinases, tumor growth, uterine myometrium, leiomyoma
Study Type: Basic
Award: $73,237

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 and Women's Hospital
Grant No.: 5 R01 HD046226-04
Keywords: uterine fibroids, cytogenetic, uterine leiomyomata, African American women, genetics
Study Type: Translational
Award: $73,237

Although the majority of uterine leiomyomata are karyotypically normal, cytogenetic abnormalities are found in 25-40% 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.: 5 R01 HD046228-04
Keywords: estrogen receptor, immune response, recombinant adenovirus, selective estrogen receptor modulator, leiomyoma, fibroid tumors
Study Type: Basic
Award: $73, 237

The hormone dependent phenotype of uterine leiomyomata suggests that interventions targeting the estrogen receptor-signaling pathway may have therapeutic efficacy. This application 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
Grant No.: 5 R01 HD046282-04
Keywords: leiomyoma, tumor suppressor gene, estrogen receptor signaling, fibroid tumors, genetics
Study Type: Basic
Award: $73,237

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
Grant No.: 5 R01 HD046251-04
Keywords: estradiol, extracellular matrix, gene interactions, smooth muscle, fibroid tumors, estrogen
Study Type: Basic
Award: $73,237

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
Grant No.: 5 R01 HD046227-04
Keywords: smooth muscle, obesity, hypertension, African American women, fibroid tumors
Study Type: Basic
Award: $73,237

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
Grant No.: 5 R01 HD046249-04
Keywords: cytoxic gene therapy, dietary, estrogen alpha-receptor antagonist, gonadotropin releasing hormone agonist, leiomyoma, fibroid tumors
Study Type: Basic
Award: $73,237

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
Grant No.: 5 R01 HD046260-04
Keywords: aromatase expression, estrogen biosynthesis, myometrium, fibroid tumors
Study Type: Basic
Award: $73,237

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: *Intermediate Outcomes of Hysterectomy and Alternatives* AHRQ
P.I.: Miriam Kuppermann, Ph.D.
Institution: University of California, San Francisco
Grant No.: 5 R01 HS11657-05
Keywords: hysterectomy, quality of life, pelvic pain, endometriosis, fibroid tumors, chronic pain conditions, decision making, hysterectomy, uterus disorder, chronic pain, endometriosis, leiomyoma, urinary incontinence, women's health
Study Type: Outcomes Research
Award: $244,125

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 to 1) determine whether and how intermediate-term (4-8 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. 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 four years of follow-up data on over 976 women. The increased sample at four 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 40?s to menopause, including intermediate-term, face this decision, 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 decision making 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: *Pregnancy and Drug Metabolizing Enzymes and Transporters (OPRU)* NICHD
P.I.: Steve N. Caritis, M.D.
Institution: Magee-Womens Research Institute, Pittsburgh
Grant No.: 5 U10 HD047905-03
Keywords: women, pregnancy, drugs, drug metabolism and transport, clinical trials, genetics
Study Type: Basic, Clinical
Award: $150,000

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 8000 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 (OPRU)* NICHD

P.I.: Menachem Miodovnik, M.D.
Institution: Georgetown University, Washington, DC
Grant No.: 5 U10 HD047890-03
Keywords: women, pregnancy, drugs, epilepsy, anticonvulsants, clinical trials, genetics
Study Type: Basic, Clinical
Award: $50,000

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, 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 (GU) (lead agency) and George Washington University (GWU) with the clinical strengths of MedStar Health (Washington Hospital Center [WHC] and Georgetown University Hospital [GUH]), GWU Hospital, and Children's National Medical Center (CNMC). 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 multi-center 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: *UW Obstetric-Fetal Pharmacology Research Unit (OPRU)* NICHD
P.I.: Mary F. Hebert, Pharm.D.
Institution: University of Washington
Grant No.: 5 U10 HD047892-03
Keywords: women, pregnancy, drugs, diabetes, anti-diabetes drugs, drug metabolism, clinical trials, genetics
Study Type: Basic, Clinical
Award: $50,000

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 following 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 (OPRU)* NICHD
P.I.: Gary D. Hankins, M.D.
Institution: University of Texas Medical Branch, Galveston
Grant No.: 5 U10 HD047891-03
Keywords: women, pregnancy, drugs, diabetes, anti-diabetes drugs, clinical trials
Study Type: Basic, Clinical
Award: $50,000

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 (SNPRC) 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 RFA 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: *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
Grant No.: 5 U54 HD041748-04
Keywords: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, genetics, minority health
Study Type: Basic, 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: *MMC/PSU Cooperative Center for Research in Reproduction* NICHD
P.I.: Ponjola Coney, M.D.
Institution: Meharry Medical College, Memphis, TN
Grant No.: 5 U54 HD044315-04
Keywords: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, fibroid tumors, estrogen
Study Type: Basic, 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: (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: *Mechanisms of aPL Antibody-Induced Pregnancy Loss* NIAMS
P.I.: Jane E. Salmon, M.D.
Institution: Hospital for Special Surgery, New York, NY
Grant No.: 2 R01 AR38889-15
Keywords: antiphospholipid antibody syndrome, autoantibodies, autoimmune disease, miscarriage, complement
Study Type: Basic, Interdisciplinary
Award: $97,650

The antiphospholipid syndrome (APS), characterized by thrombosis and pregnancy loss that occurs in the presence of antiphospholipid (aPL) antibodies, is a leading cause of miscarriage and maternal and fetal morbidity. Pregnancy complications in women with APS include fetal death, preeclampsia, and intrauterine growth restriction (IUGR). The pathogenic mechanisms that lead to injury in vivo are incompletely understood and the therapy for pregnant women with APS is only partially successful. Our studies in a murine model of APS, induced by passive transfer of human Apl antibodies, indicate that complement activation plays an essential and causative role in fetal loss and growth restriction. In addition, treatment with heparin, the standard therapy for pregnant patients with APS, prevents complement activation and protects mice from pregnancy complications induced by aPL antibodies, while anticoagulants that do not inhibit complement do not protect pregnancies. These studies indicate that APS is an inflammatory disease and, they suggest that complement inhibitory therapy might be an effective treatment. Our overall goals are to use the murine model of APS to determine how complement is activated, which complement products mediate the clinical complications associated with aPL antibodies, and the relative role of complement activation within the overall inflammatory cascade. In addition, we propose to test the hypothesis that activation of complement at the maternal-fetal interface plays an etiologic role in IUGR. The aims are: Aim 1. To determine which complement components and receptors are necessary or sufficient to mediate aPL antibody-induced placental injury, fetal loss and/or IUGR. (a) To identify the pathways that initiate complement activation and lead(s) to complement deposition in deciduas and poor pregnancy outcomes; (b) To identify the complement activation products and receptors that mediate fetal injury; (c) To assess the role of murine complement regulatory proteins in the control of local complement activation. Aim 2. To define the role of aPL antibody-mediated complement activation within the overall inflammatory cascade in order to identify complement-dependent vs. complement-independent mechanisms, (a) To define the contribution of FcγR to aPL antibody-mediated injury; (b) To define the cellular and cytokine mediators which contribute to complement activation in deciduas, to IUGR and to fetal loss. The proposed study, together with their ongoing work to define the role of complement and cytokines in pregnancy complications in APS patients, will provide insights into the mechanisms by which complement induces disease and define targets for interventions to prevent aPL antibody-associated fetal demise and IUGR. Additionally, understanding how aPL antibodies "cause" pregnancy loss may translate into new concepts about maternal-fetal tolerance and miscarriages in general and benefit women with non-aPL-related pregnancy complications.

APPENDIX D
Ad Hoc Trans-NIH Working Group for Research on Chronic Fatigue Syndrome

Eleanor Hanna, Ph.D. *Chair*	ORWH
Rebecca Costello, Ph.D.	ODS
Thomas Esch, Ph.D.	NIAID
Jerry Flanzer, D.S.W.	OBSSR
Laurie Foudin, Ph.D.	NIAAA
John D. Harding, Ph.D.	NCRR
Lynne M. Haverkos, M.D.	NICHD
J. Terrell Hoffeld, Ph.D.	CSR
Annette Kirshner, Ph.D.	NIEHS
Kathy Mann Koepke, Ph.D.	NINR
John Kusiak, Ph.D.	NIDCR
Cheryl McDonald, M.D.	NHLBI
David M. Morens, M.D.	NIAID
Peter Muehrer, Ph.D.	NIMH
Richard Nahin, Ph.D.	NCCAM
Linda Porter, Ph.D.	NINDS
Joyce Rudick	ORWH
Matthew V. Rudorfer, Ph.D.	NIMH
Denise Russo, Ph.D.	OD
Susanna Serrate-Sztein, Ph.D.	NIAMS
Susan Solomon, Ph.D.	OBSSR
Michael Twery, Ph.D.	NHLBI

APPENDIX E

Ad Hoc Tracking and Inclusion Committee, FY 2005

Office of the Director

Office of Research on Women's Health
Vivian W. 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

Fogarty International Center
Aron Primack*

National Cancer Institute
Gail Blaufarb,* 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 Biomedical Imaging and Bioengineering
Anthony Demsey,* Casey Goode

National Institute of Child Health and Human Development
Eugene Hayunga,* Sandi Delcore

National Institute on Deafness and Other Communication Disorders
Lana Shekim,* Castilla McNamara

National Institute of Dental and Craniofacial Research
Richard Mowery,* Trenita Davis

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee.

National Institute of Diabetes, Digestive and Kidney Disorders
Patricia Robuck,* Lauren Meskill, Donna James, Diane Breckenridge

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,* Sue Kennel, Ernesto Marquez, Dawn Corbett, Kathleen O'Leary

National Institute of Neurological Disorders and Stroke
Frances Yee,* Kristy Woolbert

National Institute of Nursing Research
Paul Cotton,* 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 Bower*

National Center for Research Resources
Sheila McClure,* Delores Lee, Patricia Newman, Stephen Seidel, Louise Ramm

National Center on Minority Health and Health Disparities
Ivy Chan, Derrick Tabor

Center for Scientific Review
Anita Miller Sostek*

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee

Ad Hoc Tracking and Inclusion Committee, FY 2006

Office of the Director

Office of Research on Women's Health
Vivian W. Pinn (Co-Chair), Angela Bates, Lisa Begg, Joyce Rudick
Office of Extramural Research
Carlos Caban,* Viktoriya Anufriyeva, Maria Koshy, Peter Pruesch
Office of Acquisition, Management and Procurement
Barbara Levy

Fogarty International Center
Aron Primack,* Shena Wilson

National Cancer Institute
Gail Blaufarb,* Marilyn Gaston, Kim Witherspoon, Lisa Krueger, Clarissa Douglass

National Eye Institute
Lore Anne McNicol,* William Darby, Pavi Miskala

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
Robin Barr,* Karen Bashir, Kate Nagy

National Institute on Alcohol Abuse and Alcoholism
Dorita Sewell,* Van Van, Patricia Powell

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,* Frank Cromwell

National Institute Biomedical Imaging and Bioengineering
Andrea Brooks,* Anthony Demsey

National Institute of Child Health and Human Development
Eugene Hayunga,* Sandi Delcore

National Institute on Deafness and Other Communication Disorders
Castilla McNamara,* Lana Shekim

National Institute of Dental and Craniofacial Research
Maria Canto,* Trenita Davis

National Institute of Diabetes, Digestive and Kidney Disorders
Patricia Robuck,* Christine Densmore, Lauren Meskill, Garman Williams

* Indicates the IC Lead Representative to the Tracking and Inclusion Committee

APPENDIX F

Office of Research on Women's Health Special Projects, FY 2005 and 2006

FY 2005 SPECIAL PROJECTS

- Title: *Governors' Spouses Initiative to Curb Underage Drinking* NIAAA
  NIAAA Award: $100,000
  Contact: Ting-Kai Li, M.D., Director
  NIAAA

  The ORWH supported a national initiative titled Leadership to Keep Children Alcohol Free. The ORWH's continued support has been extremely important to the Leadership initiative in continuing activity at both the state and national levels. Not only has the 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.

- Title: *Sister to Sister: Everyone Has a Heart*
  Award: $20,000
  Contact: Joyce Rudick
  ORWH

  The Sister to Sister Foundation reported a successful kickoff for the Woman's Heart Day Campaign. More than 21,300 people attended this event. Of those who attended, 8,368 were screened for risk factors for heart disease. The Foundation was also pleased to report that there were 324,902,354 media impressions of the event from across the country. Three unexpected pieces of news were released: (1) the 2006 campaign will be expanded from two months to six months, (2) the Today Show and Good Morning America Show promoted the campaign, and (3) the international component of the initiative was launched in Washington, DC, on January 27, 2005. On February 18, 2005, 8,208 women were screened in 12 cities across the U.S. with half of those screened between the ages of 40 and 60. Of those screened, 63 percent were found to have HDL cholesterol (the "good" cholesterol) lower than 60 mg/dl; 64 percent had a body mass index greater than the acceptable level of 24.9; 56 percent had blood pressure greater than the acceptable level of 120/80 mm/hg, putting them at risk for heart disease. Approximately 44 percent of those with high cholesterol did not know they had this risk factor. Roughly half of those screened had two or more major risk factors.

- Title: ORWH Web Site OIT
  OIT Award: $57,200
  Contact: Laura Curtis
  OIT

  Activities performed under this memorandum of understanding (MOU) for the redesign of the ORWH Web site include:
  - Redesign the current ORWH Web site for Section 508 compliance;
  - Determination of changes needed to address "look and feel" issues based on ORWH input;

- Preparation of the site content layout based on usability design provided by the ORWH;
- Conversion of the content on the existing ORWH Web site to newly redesigned website; and
- Launching of the new Section 508 compliant Web site.

▶ Title: *Committee on Understanding Premature Birth* IOM
IOM Award: $10,000
Contact: Joyce Rudick
ORWH

An IOM committee defined and addressed the health-related and economic consequences of premature birth. The broad goals of the study were to: (1) describe the current state of the science with respect to premature birth; (2) address the broad costs to children and their families, including economic, medical, social, psychological, and educational costs; and (3) establish a framework for action in addressing the range of priority issues, including a research and policy agenda for the future. Other sponsors included the March of Dimes, National Institutes of Health, Centers for Disease Control and Prevention, Office of Minority Health and Office of Women's Health at the Department of Health and Human Services, Health Resources and Services Administration, Department of Housing and Urban Development, Environmental Protection Agency, W.K. Kellogg Foundation, and the Pew Charitable Trusts.

▶ Title: *Update–Women of Color Health Data*
Award: $69,080
Contact: Joyce Rudick
ORWH

The purpose of this project was to revise and update the Women of Color Health Data Book, which was developed under 263-MD-633273. This update provides information on the current status of health conditions in women of color. Many changes have occurred since the second edition was published in 2003, and it is critical that the ORWH disseminate current data on patterns of disease as they differ across the diverse racial and ethnic subgroups in America. Differences in knowledge, attitudes, and beliefs impact on health behaviors and practices and on disease outcomes. There are a few data sources from which people can obtain comprehensive information on the health of women, and there are even fewer on culturally diverse racial and ethnic subgroups of women. It is important that information on other factors that impact health, such as social and economic conditions, education, or access to health services, be presented and their associations with health outcomes defined.

FY 2006 SPECIAL PROJECTS

- Title: *Sister to Sister: Everyone Has a Heart*
  Award: $20,000
  Contact: Joyce Rudick
  ORWH

  The Sister to Sister Foundation reported that the 2006 Woman's Heart Day Campaign was a success. In all, there were more than 31,172 attendees. Of those who attended, 10,416 were screened for cardiac risk factors. The Foundation was also pleased to report that there were 400,014,000 media impressions from across the country. On February 17, 2006, women were screened in 14 cities across the U.S. with 46 percent of those screened between the ages of 40 and 60; 68 percent of those screened had HDL cholesterol (the "good" cholesterol) lower than 60 mg/dl; 70 percent had a body mass index greater than the acceptable level of 24.9; 55 percent had blood pressure greater than the acceptable level of 120/80 mm/hg, putting them at risk for heart disease. About 41 percent had at least one major risk factor.

- Title: ORWH Resource Guide
  My Health. My Year. My Future
  Contact: Terri Kendrix

  This publication will be distributed through the U.S. and will have an impact on the lives of all women and their families. The Resource Guide brings disparate women's health documents together into one easy-to-use tool. It contains messages that health care professionals want to get to their patients to improve their health, prevent health problems, and lower health care costs. It will provide reliable, current information to women about common health problems and concerns as well as how to prevent or manage these health problems in an easy-to-read format that explains health problems and concerns constructively so they will be encouraged to take practical steps to improve their health. This publication is unique because it responds to the limited time women have in their daily lives by providing concise, relevant health information. Moreover, by taking positive steps toward healthier lifestyles and increased life span, women themselves will benefit. This benefit may translate into an overall reduction in national health care costs. The publication supports Healthy People 2010 goals to increase life expectancy and improve the quality of life, the Department's Steps to a Healthier U.S. to help Americans live longer, better, and healthier lives, and key NIH public health education campaigns, such as the NHLBI's The Heart Truth for Women and the NIDDK's Small Steps. Big Rewards. Prevent Type 2 Diabetes.

- Title: *Committee on Women in Science and Engineering and Public Policy* NAS
  NAS Award: $225,000
  Contact: Joyce Rudick
  ORWH

  The NIH and the ORWH supported the National Academy of Sciences Committee on Women in Science and Engineering and Public Policy study, Beyond Bias and Barriers: Fulfilling the Promise of Women in Academic Science and Engineering. The Committee's report was released in September 2006. The report outlined findings and recommendations to correct the inequities for women in these careers. The report had several key findings. Women have the ability and drive to succeed in science and engineering. Women who are interested in science and engineering careers are lost at every educational transition. The problem is not simply the pipeline. Women are very likely to face discrimination in every field of science

and engineering. A substantial body of evidence establishes that most people—men and women—hold implicit biases. Evaluation criteria contain arbitrary and subjective components that disadvantage women. Academic organizational structures and rules contribute significantly to the underuse of women in academic science and engineering. The consequences of not acting will be detrimental to the nation's competitiveness. The Committee also made several recommendations. Trustees, university presidents, and provosts should provide clear leadership in changing the culture and structure of their institutions to recruit, retain, and promote women—including minority women—into faculty and leadership positions. Deans and department chairs and their tenured faculty should take responsibility for creating a productive environment and immediately implement programs and strategies shown to be successful in minimizing the effect of biases in recruiting, hiring, promotion, and tenure. University leaders should work with their faculties and department chairs to examine evaluation practices to focus on the quality of contributions and their impact. Professional societies and higher education organizations should consider forming an interinstitution monitoring organization. Federal funding agencies and foundations should ensure that their practices—including rules and regulations—support the full participation of women and do not reinforce a culture that fundamentally discriminates against women. Federal agencies should lay out clear guidelines, leverage their resources, and rigorously enforce existing laws to increase the science and engineering talent developed in this country. Congress should take steps necessary to encourage adequate enforcement of antidiscrimination laws, including regular oversight hearings to investigate the enforcement activities of government agencies.

APPENDIX G
Office of Research on Women's Health Conferences and Workshops, FY 2005 and 2006

ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FY 2005

- Title: *NIH Family Hormonal Health Symposium: Pituitary Disorders*
  Contact: Eleanor Z. Hanna, Ph.D.

  At the beginning of FY 2005, the ORWH, in conjunction with the NICHD, the Pituitary Network Association, and the National Naval Medical Center, convened a symposium on hormonal health. The purpose of the symposium was to increase awareness and scientific understanding of pituitary disorders to promote early diagnosis, disseminate knowledge on state-of-the-art treatments, and pique the interest of the research community about the pathophysiology of these complex disorders and their many ramifications. Abnormal hormone production caused by tumors of the pituitary gland has severe and debilitating effects on growth, reproductive and sexual function, and neuroimmune function as well as devastating effects on the patient's psychological state and psychosocial interactions. Findings from this meeting were incorporated into an ORWH publication titled Family Hormonal Health, which is currently being printed.

- Title: *Advances in Uterine Leiomyoma Research: Second NIH International Congress* ORWH
  Contact: Lisa Begg, Dr.P.H., R.N.

  Uterine leiomyoma (fibroids) are the most common gynecologic neoplasm in women of reproductive age. As the number-one cause of hysterectomy, they have a profound negative impact on women's health. Uterine leiomyoma are hormonally dependent and, as such, are a potential target for endocrine-active compounds in the environment. The conference was sponsored by the ORWH and the NIEHS, as well as other NIH ICs and other Federal agencies. The goal of this conference was to bring together researchers working in the fields of biomedicine, epidemiology, basic research, therapeutics, and translational medicine to foster an exchange of scientific information on uterine leiomyoma research. The conference, which was organized by the ORWH, brought together both the research and health care communities. Participants represented academia, medicine, industry, and government, including scientists from the AHRQ. Topics addressed at the conference covered clinical experience and therapeutic strategies, epidemiology, clinical trials, pathogenesis of smooth muscle tumors, and molecular and genetic characteristics. This conference provided a forum to update the scientific agenda on leiomyoma research.

- Title: *Health Disparities in Infertility* NICHD
  Award: $5,000
  Contact: Joan Davis

  This conference, which was organized by the NICHD and co-sponsored by the ORWH, addressed infertility. According to reports from the American Society for Reproductive Medicine, infertility is a major public health problem that affects up to 10 percent of Americans of reproductive age. However, very few studies have looked at the prevalence of infertility and receipt

of related services by minority and low-income populations. This conference brought together clinicians from the NICHD's reproductive sciences portfolio and demographers from the Demographic and Behavioral Sciences Branch (DBSB) portfolio to discuss research issues, which are summarized in the conference report. The NICHD plans to convene another meeting of a broader representation of scientists working in infertility to assess the state of the science on this topic. The NICHD encourages interdisciplinary collaborations.

- Title: *Fourth International Symposium on the Intraductal Approach to Breast Cancer* — NCI
  Award: $5,000
  Contact: Doris Browne, M.D., M.P.H.

This symposium was designed to encourage experts from a variety of relevant fields to bring their knowledge to bear on issues related to abnormalities found in intraductal cells associated with invasive breast cancer. The conference was sponsored by a number of organizations, including the Susan Love Foundation, the NCI, and the ORWH. The Susan Love Foundation is making an effort to reduce the impact of breast cancer by facilitating the dissemination of research findings and by supporting innovative research responsive to the breast cancer constituency at-large. The meeting included presentations from an active and growing network of investigators working on intraductal approaches to studying breast cancer. This symposium was part of a series of meetings to address this important topic.

- Title: *Sixth International Symposium on Osteoporosis* — NIAMS
  Award: $2,500
  Contact: William Sharrock

This meeting was sponsored by a number of organizations, including the NIAMS and the ORWH, and was convened in Washington, DC. The main goal of this conference was to gather individuals interested in the treatment, research findings, and public health issues related to osteoporosis. Presenters shared their latest research findings and discussed important issues related to treatments that may be developed in the future as well as new public health directions for osteoporosis.

- Title: *Fourth International Conference on Cervical Cancer* — NCI
  Award: $5,000
  Contact: Ted Trimble

This conference on cervical cancer was organized by the NCI and sponsored by a number of organizations, including the ORWH. The goal was to provide an update on research in cervical cancer by bringing together leaders from the multiple disciplines involved with all aspects of cervical cancer causation, prevention, and screening. Objectives of the conference included:

- Description of the molecular epidemiology of cervical cancer;
- Discussion of optical techniques for screening and detection of cervical cancer;
- Description and discussion of chemoradiation for cervical cancer; and
- Enumeration and discussion of behavioral interventions for cervical cancer.

▶ Title: *Addressing Health, Educational, and Socioeconomic Disparities of Children in Immigrant Families* NICHD
Award: $5,000
Contact: Rebecca Clark, Ph.D.

The purpose of this workshop, which was organized by the NICHD with support from the Office of Behavioral and Social Science Research (OBSSR) and the ORWH, was to encourage interdisciplinary research on children in immigrant families. Social scientists contributed to a number of areas related to this topic, including legal and policy constraints related to access to health care; important ethnic, cultural, linguistic, and economic differences across racial/ethnic groups; patterns of migration into and within the U.S.; and issues affecting children's access to health care and education. Developmental scientists addressed children's developmental trajectories, including individual variation in development and age-specific language skills. Research on children from immigrant families could be enhanced if the expertise of both social scientists and behavioral scientists are included in that research.

▶ Title: *Gordon Research Conference on Calcium Signaling* NIDCR
Award: $36,795
Contact: John Kusiak, Ph. D.

This biennial conference was convened in association with the complementary meeting of the Federation of the American Societies for Experimental Biology (FASEB) and received support from the NIH, including the ORWH. The conference location alternates between Europe and the U.S. This conference on calcium signaling provided a premier forum for scientists from diverse backgrounds to review exciting new developments in this area of research. The program included presentations from those scientists who were most active in the field but who had not presented at the most recent meeting of the Gordon Research Conferences or FASEB. The size of this conference was limited to 140 to emphasize and facilitate interactive discussions and lively scientific debate. There were eight break-out sessions with chairs selected to promote active discussion and one plenary session. Posters were a key feature of the conference. Most attendees presented posters during afternoon sessions; eight posters were selected for presentation as a talk. The focus of the conference was on the structure and function of proteins involved in calcium signaling and how they relate to our understanding of disease states. Sessions were devoted to the spatial organization of calcium signaling, the structure and function of intracellular and plasma membrane calcium channels, the roles of TRP proteins in normal and disease states, the roles of calcium in secretion and vascular function, and decoding calcium signals. These topics are of important to a range of diseases and conditions, including neurodegenerative and cardiovascular disease, aging, cancer, sensory disorders, and immunological diseases.

▶ Title: *Sjögren's: Transition from Autoimmunity to Lymphoma* NIDCR
Award: $5,000
Contact: Sven-Ulrik Gorr, Ph.D.

The workshop on Sjögren's syndrome was organized by the Sjögren's Syndrome Foundation and was co-sponsored by several organizations, including the NIDCR, NCI, NIAID, the Office of Rare Diseases (ORD), and the ORWH, as well as several private-sector organizations. This workshop focused on basic research on this syndrome. It was designed to foster the exchange of scientific data and catalyze discussions about potential triggers in the transition from autoimmunity to lymphoma. It also sought to generate fresh and novel concepts by bringing in speakers from a variety of related fields, including researchers in immunology, autoimmunity, and oncology. A clinical overview of the current treatment and knowledge about the close link between

Sjögren's and lymphoma set the stage for subsequent discussions about basic scientific questions surrounding that link. To inspire young investigators to undertake basic research related to the lymphoma-autoimmune transition, each speaker was invited to select a particularly talented investigator from his or her laboratory to attend and participate in workshop discussion and present posters during a special session.

- Title: *North American Integrative Medicine Conference* CCAM
  Award: $3,000
  Contact: Richard Nahin

  The intent of this conference was to present the highest quality, peer-reviewed research in the field of complementary and alternative medicine (CAM). It was considered a major forum for CAM researchers in North America to gather and exchange ideas and data. The conference was sponsored by a number of organizations, including the NCCAM and the ORWH, and was attended by more than 600 researchers and CAM practitioners. The conference showcased original scientific research through keynote and plenary presentations, oral and poster presentations, and innovative interactive sessions. Presentations addressed basic science, clinical research, research methods, health services research, and education as it relates to CAM.

- Title: *The 10th Annual John W. Diggs Lecture* NIH OD
  Award: $500
  Contact: Sharon Jackson

  The ORWH provided support for support for the production of the awards presented at this annual lecture.

ORWH-SUPPORTED CONFERENCES AND WORKSHOPS, FISCAL YEAR 2006

- Title: *The Women's Health Initiative (WHI) Legacy to Future Generations of Women*

This conference was sponsored in conjunction with the NHLBI and the ORWH and was convened in Bethesda, MD, on the NIH campus. The WHI is a landmark study in women's health and has important public health implications about the menopause and aging for women now as well as for future generations of women. This conference addressed many important findings from this study and included all center directors and PIs associated with this study. Topics addressed at this conference included:

- Presentations on the results for the WHI dietary modification and calcium/vitamin D clinical trials;
- Findings from the two hormone trials, which had been released earlier;
- A synthesis of complex information generated from the WHI observational study and all four clinical trials;
- Discussions about the significance of the WHI findings for postmenopausal women's health;
- Recognition of important contributions made by more than 161,000 women who participated in the WHI; and
- Overview of future WHI efforts, including opportunities for scientific collaboration, analysis of biospecimens, and the WHI Extension Study.

- Title: *Developing New Standards for Autoantibody Measurement: Bringing Metrology to Serology* NCI
  Award: $5,000
  Contact: Joy Osborn

Two of the largest health problems in the U.S. are autoimmune diseases and cancer, which, when combined, affect almost half of all Americans. Measuring circulating autoantibodies is an important part of clinical medicine, and there are many FDA-approved autoantibody tests that are currently available. The central technical feature shared by all autoantibody diagnostic assays is the capture of autoantibodies from serum using immobilized autoantigen. However, substantial variability in these tests has led to confusion about results and, therefore, questions concerning their utility in the diagnosis of disease. Currently, there are no autoantigen standard reference materials or standardized protocols. Moreover, there is little coordination between diagnostic developers, clinicians, and regulators regarding standards and best practices related to these tests. This workshop, which was convened by the National Institute on Standards and Technology (NIST), brought together leaders in autoantibody diagnostics, diagnostic testing, clinical laboratory medicine, and regulatory affairs to identify the fundamental and common metrology issues that underpin most antibody-based serodiagnostics. In addition, the workshop fostered partnerships and collaborations to develop the infrastructure and science needed to improve autoantibody-based diagnostics. This workshop was sponsored by the NIST, the NCI, the ORWH, and the American Autoimmune Disease Association.

- Title: *Indigenous Suicide Prevention Research Programs in Canada and the United States* — NIMH
  Award: $2,500
  Contact: Jane Pearson

  This conference was organized by the NIMH, the Indian Health Service, Health Canada, and the Canadian Institutes of Health and held in Albuquerque, NM. It was supported by a number of sponsors, including the NIH ORD, the ORWH, the OBSSR, NIDA, the NIAAA, and the National Library of Medicine (NLM), as well as other U.S. agencies, such as the Substance Abuse and Mental Health Services Administration (SAMHSA). The conference brought together representatives from research, service, community programs, and governments from a range of countries, tribes, and villages located in Canada, the U.S., and U.S. territories. Presentations illuminated the current state of knowledge concerning indigenous people and efforts related to suicide prevention. While suicide rates in young, indigenous males are among the highest in the U.S. and Canada, the rates vary dramatically across communities. Conference attendees were asked to address what research efforts, from the communities' perspectives, are need to better address this tragic outcome that is very relevant to health disparities. Participants established a communication network to continue to share information about suicide and suicide prevention.

- Title: *Progesterone Receptor Modulators and the Endometrium: Changes and Consequences* — NCI
  Award: $5,000
  Contact: Ted Trimble

This conference was organized by the NCI and convened in Bethesda, MD. The goal was to develop recommendations for regulatory interpretation of endometrial changes with chronic progesterone receptor modulator (PRM) treatment and to discuss what these recommendations might mean for future research. Questions were raised related to the validity of the concept of unopposed estrogen (E2) as an interpretation of endometrial response to treatment with PRMs. Conference topics included a review of the evidence regarding endometrial safety, classification of PRM endometrial effects, and methods to monitor endometrial safety in clinical trials and in clinical practice.

- Title: *Meharry-Vanderbilt Alliance 4th National Health Disparities Conference: Why Our Babies Die* — NICHD
  Award: $3,000
  Contact: Uma Reddy

  This three-day conference attracted approximately 200 investigators and physicians from across the country to discuss current research efforts on the disparities of infant mortality and morbidity in the U.S. This conference, Why Our Babies Die, was convened in Nashville, TN, and emphasized prevention efforts. Tennessee is ranked 48th in the nation in infant survival, and the state's preterm birth rate is 47th in the U.S. Members of the local research and clinical population wanted to address these critical problems at this conference. This conference was sponsored by the NICHD, the ORWH, and other NIH entities as well the March of Dimes, Adeza Biomedical, Matria Healthcare, and Governor's Office of the State of Tennessee. This support was critical to keep registration fees low for the many attendees from nonprofit agencies and health centers that serve medically underserved communities.

▶ Title: *Regulation of Inflammatory Responses: Influence of Sex and Gender* — NIAID, ORWH
Contact: Christopher Taylor, Lisa Begg

This workshop, which was co-sponsored by the ORWH and the NIAID, focused on the regulation of inflammatory responses and the influence of sex and sex-steroids on inflammatory responses. Managing these responses may influence disease risk. Participants at this workshop evaluated existing knowledge and concepts related to inflammation with the goal of developing innovative approaches to the prevention and treatment of acute and chronic diseases. They identified gaps in knowledge and research questions to be addressed in future research.

▶ Title: *Fifth International Symposium on Hormonal Carcinogenesis* — NCI
Award: $5,000
Contact: Suresh Mohla

This symposium focused on hormonal carcinogenesis in breast, prostate, ovarian, endometrial, colon, and lung cancers. INSERM, the French national health and medical research institute, organized the meeting and received support from the NCI and other organizations. It was held in Montpellier, France. The symposium addressed: (1) cellular origins of endocrine-related cancers; (2) mitotic kinases, centrosome amplification, and genomic instability; (3) new developments in steroid-receptor interactions; (4) risk assessment and relevant biomarkers for early disease; (5) novel strategies for prevention and treatment of endocrine-related cancers; (6) hormone dependency versus hormone independency; and (7) emerging fields in hormones and colorectal and lung cancers. Three state-of-the-art lectures were given during this conference. These lectures were titled Self-Renewal and Cancer Stem Cells, Ovarian Cancer: Linking Genomics to New Target Discovery and Molecular Markers: the Way Ahead, and Aurora, Polo, Nek, Cdk1 the Mitotic Bodyguards. Dr. Vivian W. Pinn, Director of the ORWH, gave a special lecture on Women's Health Research: Perspectives from the National Institute of Health.

▶ Title: *FMR1 Premutation and Premature Ovarian Failure: Worldwide Community Guideline Development* — NICHD
Award: $5,000
Contact: Larry Nelson

Increasingly, clinicians are responsible for engaging patients in discussions regarding available genetic tests, the results of which may have major implications for other family members. Premutations in the fragile X mental retardation 1 gene (FMR1) have been linked to altered ovarian function that may present as infertility, with low response to gonadotropin therapy, diminished ovarian reserve, or premature ovarian failure. This meeting, which was initiated by the NICHD, brought together recognized experts to present current perspectives on the management of women who may have altered ovarian function possibly related to an FMR1 premutation. Representatives from advocacy associations were invited to give presentations on community perspectives on this issue. Participants identified a need to establish standardized clinical definitions, terminology, and testing recommendations to facilitate research in this area. The meeting concluded

with an open discussion of the proposed Worldwide Community Development Guidelines.

- Title: *2006 NIDDK International Symposium: Frontiers in Painful Bladder Syndrome and Interstitial Cystitis* NIDDK
  Award: $5,000
  Contact: Griffin Rogers

  This symposium, which was organized by the NIDDK, focused on the current state of research and clinical treatment for painful bladder syndrome and interstitial cystitis. The goals of the meeting included increasing scientific awareness of interstitial cystitis and its treatments, providing a forum to discuss the definition and etiology of interstitial cystitis and painful bladder syndrome, and exchanging information and ideas on current and future research to treat this disease and its symptoms. Plenary talks, selected short talks, and a poster session provided a forum for interactions among investigators working across these areas.

APPENDIX H
Intramural Programs on Research on Women's Health Steering Committee, FY 2005 and 2006

Co-chairs

Dr. Esther Sternberg, NIMH

Dr. Barbara Vonderhaar, NCI

Members

Dr. Deborah Carper, NEI

Dr. Giovanni Cizza, NIMH

Dr. Lynn Gerber, CC

Dr. Hynda Kleinman, NIDCR

Dr. Ken Korach, NIEHS

Dr. James Lacey, NCI

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Dr. Vivian W. Pinn, ORWH

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Dr. Janine Smith, NEI

Dr. Jeffrey Struewing, NCI

Dr. Susan Wray, NINDS

Dr. Richard Wyatt, OIR

Dr. Jo Anne Zujewski, NCI

APPENDIX I
Women's Health Special Interest Group Lectures, FY 2005 and 2006

December 17, 2004

Exercise and Women's Health: Basic and Clinical Applications

Patricia Deuster, Ph.D., M.P.H
USUHS

January 28, 2005

New Molecular Epidemiology Data on HPV16 and Cervical Cancer: Studies of a Uniquely Powerful Carcinogen

Mark Schiffman, M.D., M.P.H.
NCI, NIH

March 18, 2005

Effects of Sex Hormones on Cognitive Aging

Susan Resnick, Ph.D.
NIA, NIH

April 22, 2005

Severe Combined Immunodeficiency: New Approaches, New Problems

Jennifer Puck, M.D.
NHGRI, NIH

June 24, 2005

Racial Disparities in Women's Health Care

Alicia Armstrong, M.D.
NICHD, NIH

October 28, 2005

Management of Polycystic Ovary Syndrome

Katherine Sheriff, M.D.
Drexel University

December 16, 2005

Gender Differences in Lung Function and Response to Environmental Events

Darryl Zeldin, M.D.
NIEHS, NIH

February 24, 2006

Disparity in X Chromosome Gene Dosage and the Risk for Coronary Disease

Carolyn Bondy, M.D.
NICHD, NIH

April 17, 2006

Endometriosis: New Insights into Killer Cramps

Pamela Stratton, M.D.
NICHD, NIH

May 19, 2006

A Model for Understanding the Etiology of Domestic Violence

Ted George, M.D.
NIAAA, NIH

September 22, 2006

Fertility Preservation in Women Undergoing Chemotherapy

Alicia Armstrong, M.D., M.H.S.C.R.
NICHD, NIH

APPENDIX J
Office of Research on Women's Health Women's Health Seminar Series

November 4, 2004

Women and Obesity

Introduction to Obesity in Women: Special Needs, Problems, Epidemiology
Robert Kuczmarsky, Dr.P.H.
NIDDK, NIH

Obesity and Eating Disorders in Adolescents (Prevention)
S. Bryn Austin, Sc.D.
Children's Hospital Boston

Weight Gain Prevention in Women in Midlife
Lewis Kuller, M.D., Dr.P.H.
University of Pittsburgh

Obesity and Stigma
Marlene Schwartz, Ph.D.
Yale University

March 31, 2005

Women and Sleep Disorders

Sleep Disturbances during Menstrual Cycle and Pregnancy
Kathryn Lee, R.N., Ph.D., F.A.A.N.
University of California, San Francisco

Sleep Disturbances during Midlife and Older Age: What Next?
Terry Young, Ph.D.
University of Wisconsin, Madison

The Lived Experience: The Patient Perspective
M. Elizabeth Johns
Apex, Inc.

Clinical Approaches to Women and Sleep Disorders
Barbara Phillips, M.D., M.S.P.H., F.C.C.P.
Chandler Medical Center

June 7, 2005

Women and Depression

Postpartum Depression in Pediatric Practices: Opportunities and Challenges
Linda Chaudron, M.D.
University of Rochester Medical Center

The Menopausal Transition, Sex Steroids, and Depression
Peter Schmidt, M.D.
NIMH, NIH

Cultural Issues Related to Diagnosis and Treatment of Depression for Women
Charlotte Brown, Ph.D.
Western Psychiatric Institute/Clinic

Perspectives on Women and Depression from the Community
Sue Bergeson
Depression and Bipolar Support Alliance

November 1, 2005

Women and Pain

Is Chronic Pain a Women's Health Issue?
Roger Fillingim, Ph.D.
University of Florida College of Dentistry

The Pains of Endometriosis
Karen Berkley, Ph.D.
Florida State University

Chronic Migraine and Women's Health
Richard Lipton, M.D.
Albert Einstein College of Medicine, New York

Fibromyalgia: A Personal Look at Chronic Pain
Katherine Woodbury-Harris, Ph.D.
NINDS, NIH

March 23, 2006

Women and Sexually Transmitted Infections

Gender Differences and STIs
Victoria Cargill, M.D., M.S.C.E.
Office of AIDS Research, NIH

Topical Microbicides
Roberta Black, Ph.D.
NIAID, NIH

Prevention of STIs in Adolescent Girls
Craig Cohen, M.D., M.P.H.
University of California, San Francisco

Community Perspectives on STIs among Adolescents and Young Women
Kathy Woodward, M.D.
Children's National Medical Center, Washington, DC

June 13, 2006

Caregiving

Family-Centered Service: What Is It and Why Should I Care? Lessons from Families of Children with Disabilities
Peter Rosenbaum, M.D., F.R.C.P.
McMaster University

Comparison of Emotional and Biological Parameters in Mexican American and White Male and Female Caregivers of Patients with Alzheimer's Disease
Sharon Lewis, R.N., Ph.D., F.A.A.N
University of Texas Health Science Center

Systematic Review of Advance Care Planning and Caregiver Burden and Satisfaction with Quality of Care at the End of Life
Anne Wilkinson, Ph.D., M.S.
Rand Corporation

The Task of Caregiving: Catastrophe or Celebration?
Chloe JonPaul, M.S.
National Family Caregivers Association

Acronyms

ACRONYMS USED IN THIS REPORT

AAP	American Academy of Pediatrics
ACRWH	Advisory Committee on Research on Women's Health
ADHD	Attention Deficit Hyperactivity Disorder
AEDS	Anti-Epileptic Drugs
AHRQ	Agency for Healthcare Research and Quality
AI	Aromatase Inhibitor
AIDS	Acquired Immune Deficiency Syndrome
AITRP	AIDS International Training and Research Program
ALD	Alcoholic Liver Disease
ANS	Autonomic Nervous System
APF	Anti-Proliferative Factor
ART	Anti-Retroviral Therapy
ASCB	American Society for Cell Biology
ASCO	American Society of Clinical Oncology
ASCUS	Atypical Squamous Cells of Undetermined Significance
AUDs	Alcohol Use Disorders
AWIS	Association for Women in Science
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BMD	Bone Mineral Density
BMI	Body Mass Index
BMP	Bone Morphogenetic Protein
BRCA1/2	Breast Cancer – gene mutation
BSE	Breast Self-Examination
BUFS	Breast Ultrasound Fluoroscopy System
BV	Bacterial Vaginosis
CAC	Coronary Artery Calcium
CAD	Coronary Artery Disease
CAH	Complex Atypical Hyperplasia
CAM	Complementary and Alternative Medicine
CASI	Computer-Assisted Self-Interviews
CBT	Cognitive Behavioral Therapy
CC	Clinical Center
CCD	Charged-Coupled Devices
CCRWH	Coordinating Committee on Research on Women's Health
CDC	Centers for Disease Control and Prevention
CEA	Carcinoembryonic Antigen
CFS	Chronic Fatigue Syndrome
CFSAN	Center for Food Safety and Applied Nutrition, FDA
CHD	Coronary Heart Disease
CMV	Cytomegalovirus
CNMP	Chronic Non-Malignant Pain
CRF	Corticotropin-Releasing Factor
CRP	C-Reactive Protein
CRTAP	Cartilage-Associated Protein
CSR	Center for Scientific Review
CT	Computerized Tomography
CVD	Cardiovascular Disease
CVS	Chorionic Villus Sampling

DBT	Dialectical Behavior Therapy
DCIS	Ductal Carcinoma in Situ
DDT	Dichloro-Diphenyl-Trichloroethane
DES	Diethylstilbestrol
DHHS	Department of Health and Human Services
DoD	Department of Defense
DOT	Diffuse Optical Tomography
EBV	Epstein-Barr Virus
ECC	Early Childhood Caries
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme Linked Immunosorbent Assay
EOC	Epithelial Ovarian Cancer
EPA	U.S. Environmental Protection Agency
ER	Estrogen Receptor
ESRD	End-Stage Renal Disease
FAES	Foundation for Advanced Education in the Sciences
FAP	Familial Adenomatous Polyposis
FAS	Fetal Alcohol Syndrome
FASEB	Federation of the American Societies for Experimental Biology
FDA	Food and Drug Administration
FIC	Fogarty International Center
FIRCA	Fogarty International Research Collaboration Award
f-MRI	Functional Magnetic Resonance Imaging
FOBT	Fecal Occult Blood Test
FSH	Follicle-Stimulating Hormone
FY	Fiscal Year
GAO	U.S. General Accounting Office
GBS	Group B Streptococci
GCRC	General Clinical Research Center
GDM	Gestational Diabetes
GED	Graduate Equivalency Degree
GnRH	Gonadotropin-Releasing Hormone
GPP	Graduate Partnerships Program
GVHD	Graft-Versus-Host Disease
HA	Hyaluronic Acid
HAART	Highly Active Anti-Retroviral Therapy
Hb	Hemoglobin
HBOC	Hereditary Breast Ovarian Cancer
HCV	Hepatitis C Virus
HISS	High Spectral and Spatial Resolution
HIV	Human Immunodeficiency Virus
HNPCC	Hereditary Non-Polyposis Colon Cancer
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSV	Herpes Simplex Virus
HT	Hormone Therapy
IBS	Irritable Bowel Syndrome
ICs	Institutes and Centers of the National Institutes of Health
IFN	Interferon
IHD	Ischemic Heart Disease
IL	Interleukin
IOM	Institute of Medicine

IP	Intraperitoneal
IRB	Institutional Review Board
IRP	Intramural Research Program, NIH
IRPWH	Intramural Research Program in Women's Health
IRSDA	International Research Scientist Development Award
IUGR	Intrauterine Growth Restriction
IV	Intravenous
IVF	In Vitro Fertilization
IVH	Intraventricular Hemorrhage
IWHR	Interdisciplinary Women's Health Research
JDRF	Juvenile Diabetes Research Foundation International
KOR	Kappa Opioid Receptors
KS	Kaposi's Sarcoma
LAM	Lymphangioleiomyomatosis
LC	Locus Coeruleus
LH	Luteinizing Hormone
LMP	Low Malignant Potential
LOS	Late-Onset Sepsis
LSIL	Low-grade Squamous Intra-epithelial Lesions
MTCT	Mother-to-Child HIV Transmission
MEC	Medical Executive Committee, NIH Clinical Center
MFSP	Minority Faculty Student Partnership Program
MIS	Mullerian Inhibiting Substance
MOH	Ministry of Health
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTHFR	Methylene Tetrahydorfolate Reductase
NAS	National Academy of Sciences
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
NDPA	NIH Director's Pioneer Award
NE	Norepinephrine
NEI	National Eye Institute
NES	Nonepileptic Seizures
NHL	Non-Hodgkin's Lymphoma
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Survey
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
NIH	National Institutes of Health

NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIOSH	National Institute of Occupational Safety and Health
NIST	National Institute on Standards
NLM	National Library of Medicine
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NOD	Non-Obese Diabetic
NRT	Nicotine Replacement Therapy
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSCLC	Non-Small-Cell Lung Cancer
NSF	National Science Foundation
NVP	Nevirapine
OA	Osteoarthritis
OAR	Office of AIDS Research, NIH
OBSSR	Office of Behavioral and Social Sciences Research, NIH
OC	Office of Communications, NIH
OCa	Ovarian Cancer
OCs	Organochlorine Compounds
OD	Office of the Director, NIH
ODD	Oppositional Defiant Disorder
ODS	Office of Dietary Supplements
OEODM	Office of Equal Opportunity and Diversity Management, NIH
OER	Office of Extramural Research, NIH
OI	Osteogenesis Imperfecta
OIR	Office of Intramural Research, NIH
OITE	Office of Intramural Training and Education
OLPA	Office of Legislative Policy and Analysis, NIH
OMAR	Office of Medical Applications Research
OMB	U.S. Office of Management and Budget
ORD	Office of Rare Diseases
ORWH	Office of Research on Women's Health
OSE	Office of Scientific Education, NIH
PA	Program Announcement
PBD	Proliferative Breast Disease
PBS/IC	Painful Bladder Syndrome/Interstitial Cystitis
PCBs	Polychlorinated Biphenyls
PCOS	Polycystic Ovary Syndrome
PDGF	Platelet-Derived Growth Factor
PEMF	Pulse-Electromagnetic Fields
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PET	Positron Emission Tomography
PHS	Public Health Service
PI	Principal Investigator
PID	Pelvic Inflammatory Disease
PMS	Premenstrual Syndrome
POTS	Postural Tachycardia
PR	Progesterone Receptor
PRIM&R	Public Responsibility in Medicine and Research
PTH	Parathyroid Hormone
PTSD	Posttraumatic Stress Disorder
PUFA	Polyunsaturated Fatty Acid
QD	Quantum Dots

QOL	Quality Of Life
RA	Rheumatoid Arthritis
RDC	Research Diagnostic Criteria
RDW	Red Cell Distribution Width
REAP	Research Enhancement Awards Program
RFA	Request for Applications
RFP	Request for Proposals
ROC	Receiver Operating Characteristic
RTT	Rett Syndrome
RVM	Rostral Ventromedial M
SAGE	Serial Analysis of Gene Expression
SAMHSA	Substance Abuse and Mental Health Services Administration
SCD	Sudden Cardiac Death
SCN	Suprachiasmatic Nucleus
SCOR	Specialized Centers of Research
SD	Spasmodic Dysphonia
SEER	Surveillance, Epidemiology, and End Results
SERM	Selective Estrogen Receptor Modulator
SES	Socioeconomic Status
SIDS	Sudden Infant Death Syndrome
SIL	Squamous Intraepithelial Lesion
SLE	Systemic Lupus Erythematosus
SNHL	Sensorineural Hearing Loss
SNP	Single Nucleotide Polymorphism
SoS	State of the Science
SPECT	Single Photon Emission Computed Tomography
SPORE	Specialized Programs of Research Excellence
SRA	Scientific Review Administrator
SRG	Scientific Review Group
SS	Sjögren's Syndrome
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
SUD	Substance Use Disorders
SZP	Superficial Zone Protein
TAU	Tel Aviv University
TB	Tuberculosis
TMD	Temporomandibular Disorders
TMJ	Temporomandibular joint
TMJD	temporomandibular joint and muscle disorders
TNF	Tumor Necrosis Factor
TSC	Tuberous Sclerosis Complex
UEC	Uterine Endometrioid Carcinoma
UNESCO	United Nations Educational, Scientific, and Cultural Organization
US	Ultrasound
U.S.	United States
UTI	Urinary Tract Infection
VAC	Vitex agnus-castus L. (chasteberry)
VCT	Voluntary Counseling and Testing
VEGF	Vascular Endothelial Growth Factor
VIP	Vasoactive Intestinal Peptide
VM	Ventriculomegaly
VMS	Vasomotor Symptoms
WHI	Women's Health Initiative

WHO	World Health Organization
WHSIG	Women's Health Special Interest Group
WICB	Women in Cell Biology
WRHR	Women's Reproductive Health Research
ZVD	Zidovudine

Index

A

B

C

D

E

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

U

V

W

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